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(54) Title: SUBSTITUTED PYRAZOLES HAVING CORTICOTROPIN-RELEASING FACTOR (CRF) ANTAGONIST ACTIVITY		
(57) Abstract		
<p>The compounds of formula (I) wherein A, R₁, R₃, X₁, Y and Z are as defined herein, have corticotropin-releasing factor (CRF) antagonist activity. They are useful in the treatment of illnesses induced by CRF, such as stress and anxiety related disorders.</p>		<div data-bbox="958 1144 1266 1396"></div> <div data-bbox="1347 1218 1396 1260">(I)</div>

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SUBSTITUTED PYRAZOLES HAVING CORTICOTROPIN-RELEASING FACTOR (CRF) ANTAGONIST ACTIVITY

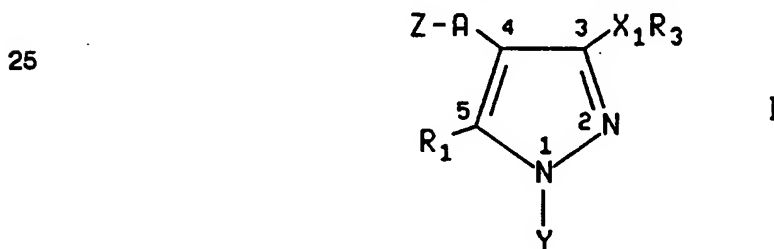
Background of the Invention

This invention relates to substituted pyrazoles, pharmaceutical compositions containing them, and their use in the treatment of stress-related and other diseases. The compounds have corticotropin-releasing factor (CRF) antagonist activity.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g. as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M.J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are considered effective in the treatment of a wide range of stress-related illnesses, such as stress-induced depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, human immunodeficiency virus (HIV) infections, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems.

Summary of the Invention

The present invention relates to a compound of the formula



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and the pharmaceutically acceptable acid addition salts thereof,
wherein

A is CH₂;

R₁ is hydrogen; linear or branched C₁-C₆ alkyl; C₃-C₆ alkyl containing one or two
35 non-adjacent double bonds; hydroxy; O(C₁-C₆ alkyl); SH; S(C₁-C₆ alkyl); SO₂(C₁-C₆ alkyl); C₃-C₆ cycloalkyl; morpholinyl; piperidinyl, or aryl which aryl may be substituted by one to three of fluoro, chloro, bromo, trifluoromethyl, hydroxy, O(C₁-C₆ alkyl), SH,

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S(C₁-C₆ alkyl), amino, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, or one of iodo, nitro or cyano, said aryl being selected from the group consisting of phenyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, and thiazolidinyl;

R₃ is linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₈ alkenyl wherein the double bond is not adjacent to X₁ when X₁ is a heteroatom, or C₃-C₇ cycloalkyl(CH₂)_n wherein n is 0 to 4, or (CH₂)_qQ₁R₁₉ wherein q is 0, 1 or 2, Q₁ is O, S, NH, N(C₁-C₆ alkyl), or a covalent bond when X₁ is not a covalent bond, and R₁₉ is hydrogen, linear C₁-C₆ alkyl, branched C₃-C₈, C₃-C₈ alkenyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl (CH₂);

X₁ is a covalent bond, CH₂, O, S, or NR, wherein R is hydrogen or linear C₁-C₆ alkyl or branched C₃-C₈ alkyl;

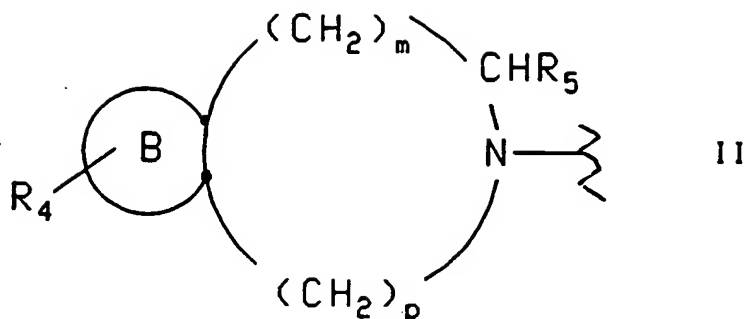
Y is phenyl which is substituted by from one to three of fluoro, chloro, bromo, formyl, C₁-C₆ alkyl, C₃-C₁₀ branched alkyl, C₁-C₆ alkoxy or trifluoromethyl, or by one of hydroxy, iodo, cyano, nitro, amino, NH(C₁-C₄ alkyl), N(C₁-C₄)(C₁-C₂ alkyl), COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂, NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C₁-C₄ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may contain one double or triple bond; thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or piperidinyl, each of which may be substituted by one to three of any one of fluoro, chloro, bromo, or methyl, or one of trifluoromethyl; and

Z is

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(a)

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10 wherein the B ring is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, or indolyl, each of which may be substituted by methyl, methoxy, trifluoromethyl, fluoro, chloro, bromo or iodo; or a saturated 5- or 6-membered carbocyclic ring or a partially unsaturated ring having one or two double bonds;

15 R_4 is hydrogen, C_1 - C_8 alkyl, C_1 - C_8 alkoxy, hydroxy, fluoro, chloro, bromo, iodo, or trifluoromethyl;

R_5 is hydrogen, linear C_1 - C_8 alkyl, branched C_3 - C_8 alkyl, C_3 - C_8 alkenyl, or $(CH_2)_o$ - X_2 -(CH_2) $_r$ - Q_2 - R_6 ;

20 X_2 and Q_2 are each independently O, S, NH, N(C_1 - C_8 alkyl), or one of X_2 and Q_2 may be a covalent bond;

R_6 is hydrogen, linear C_1 - C_8 alkyl, branched C_3 - C_8 alkyl or C_3 - C_8 alkenyl;

m is 0 or 1;

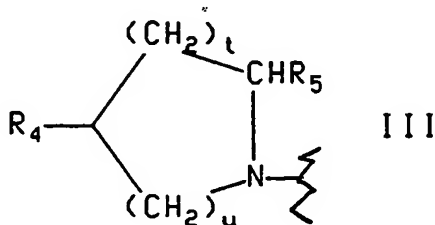
o is 1 or 2;

p is 1 or 2; and

25 r is 0, 1 or 2

(b)

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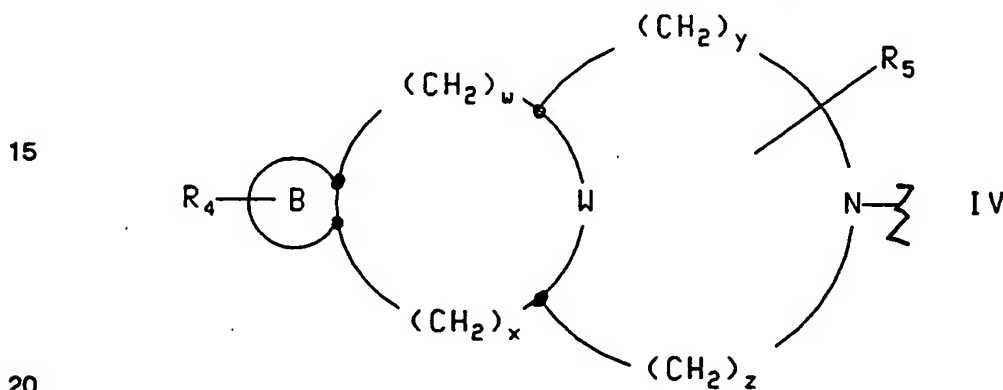


wherein R_4 and R_5 are as defined above, and t and u are each independently 1 or 2;

-4-

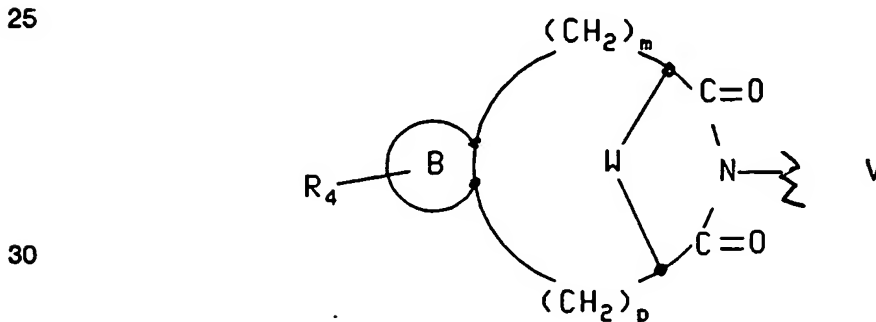
- (c) $-NR_7R_8$ wherein R_7 and R_8 are each independently hydrogen, C_1 - C_6 linear alkyl, branched C_3 - C_8 alkyl, C_3 - C_8 alkenyl, $(CH_2)_vCH_2OH$, $(CH_2)_vNR_9R_{10}$, wherein v is 0 to 3, and R_9 and R_{10} are each independently hydrogen, or linear C_1 - C_6 alkyl; $(C_3$ - C_{12} cycloalkyl) $(CH_2)_n$, $(C_6$ - C_{10} bicycloalkyl) $(CH_2)_n$, benzofused C_3 - C_6 cycloalkyl, C_1 - C_6 hydroxyalkyl, phenyl $(CH_2)_n$, each of which may be substituted by one or two of hydroxy, fluoro, chloro, bromo, C_1 - C_5 alkyl, or C_1 - C_5 alkoxy; or R_7 and R_8 may be taken together with the nitrogen to form a saturated or partially unsaturated 5- to 7-membered ring which may contain one of O, S, NH or $N(C_1$ - C_6 alkyl) and which may be substituted by C_1 - C_6 alkyl, hydroxy or phenyl wherein any double bond(s) are not adjacent to any heteroatoms; and n is 0 to 4;

(d)



wherein B , R_4 and R_5 are as defined above, w , x , y and z are each independently 1 or 2, and W is $(CH_2)_q$ wherein q is as defined above, $N(C_1$ - C_6 alkyl), or oxygen;

(e)

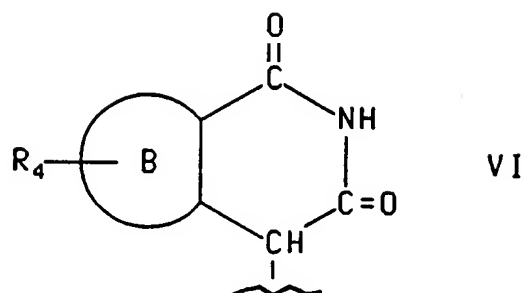


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wherein B, W, R₄, m and p are as defined above;

(f)

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VI

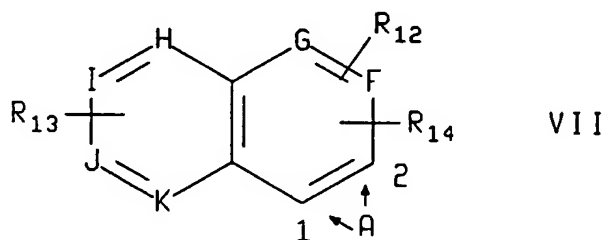
10 wherein B and R₄ are as defined above;

(g) $O(CH_2)_v R_{11}$

wherein v is 0 to 3 and R₁₁ is linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, 15 benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, or thienyl, each of which may be substituted by one or two of any one of fluoro, chloro, bromo, methyl, or trifluoromethyl;

(h)

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VII

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wherein A is as defined above and is linked to position 1 or 2 while R₄ is attached to position 2 or 1, respectively; F, G, H, I, J and K are independently C or N, provided that not more than three of H, I, J and K are N with not more than two adjacent nitrogens;

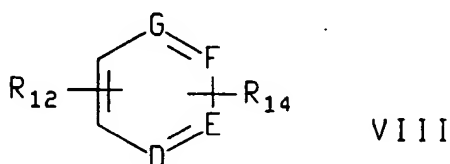
30 R₁₂ and R₁₃ each independently are hydrogen, linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₆ alkenyl, fluoro, chloro, bromo, trifluoromethyl, hydroxy, thiol, C₁-C₁₂ alkoxy, C₁-C₁₂ thioalkanyl, or C₃-C₁₂ alkenoxy or C₃-C₁₂ thioalkenyl wherein the double bond is not adjacent to the oxygen or sulfur; and R₁₄ is hydroxy, C₁-C₁₂ alkoxy, C₃-C₁₂ alkenoxy

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wherein the double bond is not adjacent to the oxygen, or $-X_2-(CH_2)_r-Q_2-R_6$ wherein X_2 , r , Q_2 and R_6 are as defined above in paragraph (a) except that Q_2 is not sulfur, or R_{14} is $NR_{15}R_{16}$ wherein R_{15} and R_{16} are each independently hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl wherein the double bond is not adjacent to the nitrogen, or C_3-C_7 cycloalkyl- $(CH_2)_n$ wherein n is as defined above, or R_{15} and R_{16} together with the nitrogen form a saturated five or six membered ring optionally condensed with benzo; or

(i)

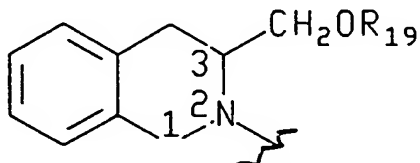
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wherein D, E, F and G are independently C or N, provided that not more than two of D, E, F and G are N, R_{12} and R_{14} are as defined above, A, defined above, is linked to a carbon in formula VIII, and R_{14} is linked to a carbon located adjacent to the carbon to which A is linked.

Preferred compounds of formula I are those wherein Z is 1,2,3,4-tetrahydroquinolin-2-yl substituted by R_5 which is $(CH_2)_6-X_2-(CH_2)_r-Q_2-R_6$, or more preferably R_5 is $(CH_2)_kOH$ wherein k is 1 to 4, or $CH_2OCH_2CH_2OR_6$. Other preferred compounds are those wherein Z is 1,2,3,4-tetrahydroisoquinolin-2-yl, wherein R_5 is substituted at position 3, and the absolute configuration at the 3-position is S or R or R,S. Further preferred compounds are those wherein Z is of the formula

25



with the absolute configuration at position 3 determined by its derivation from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline, wherein R_{19} is methyl, ethyl, isopropyl, cyclopropylmethylene, or 2-hydroxyethyl, and, more preferably, wherein in addition XR_3 is ethyl or methylthio, Y is 2,6-dichloro-4-trifluoromethylphenyl, 2,4,6-trichlorophenyl, 2,4,6-trimethylphenyl, 2,6-dimethyl-4-bromophenyl, or 2,6-dibromo-4-fluorophenyl, and R_1 is methyl or ethyl.

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More specific compounds of formula I are those wherein Z is as defined in (h), and, more specifically, A is linked to position 1, and R_{14} is at position 2 and is $X_2-(CH_2)_6Q_2R_6$; or A is linked to position 1, F, G, H, I, J, and K are each carbon, and R_{14} is 2-methoxy, 2-ethoxy, 2-isopropoxy, or 2-cyclopropylmethoxy; or

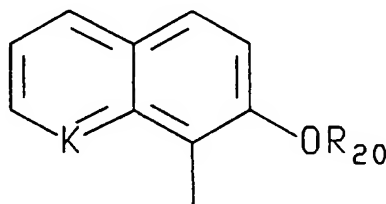
5 A is linked to position 1, K is nitrogen, F, G, H, I and J are each carbon, and R_{14} is at position 2 and is $X_2-(CH_2)_6Q_2R_6$; or

A is linked to position 1, K is nitrogen, F, G, H, I, and J are each carbon, and R_{14} is at position 2 and is methoxy, ethoxy, isopropoxy, or cyclopropylmethoxy, $HOCH_2CH_2O-$, or $CH_3OCH_2CH_2O-$; or

10 A is at position 1 and R_{14} is at position 2 and is ethoxy, isopropoxy, cyclopropylmethoxy, $HOCH_2CH_2O$ or $CH_3OCH_2CH_2O-$.

More specific compounds of formula I include those wherein Z is

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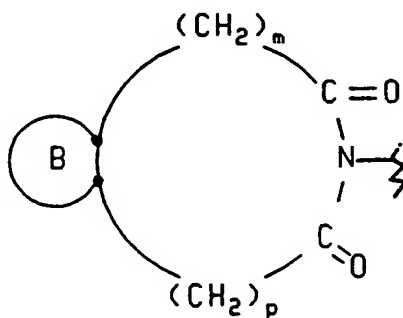


wherein K is C or N and R_{20} is methyl, ethyl, isopropyl, cyclopropylmethylene, methoxyethylene, hydroxyethylene, and, more specifically, in addition X_1R_3 is ethyl or methylthio, Y is 2,6-dichloro-4-trifluoromethylphenyl, 2,4,6-trichlorophenyl or 2,6-dibromo-4-fluorophenyl, and R_1 and R_2 are each methyl or ethyl.

20

Other more specific compounds are those of formula I wherein Z is as defined in (a), B is phenyl, p and m are each 1, and R_5 is CH_2OCH_3 or $CH_2OCH_2CH_2OH$; and those wherein Z is

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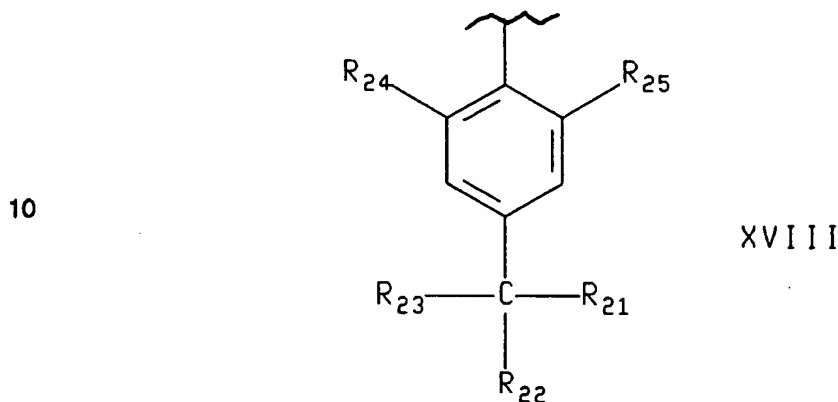


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More specific compounds of formula I of the invention include those wherein Y is phenyl substituted by three substituents one each at positions 2, 4 and 6, e.g. 2,4,6-trichlorophenyl, 2,6-dimethyl-4-bromophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 2,6-dichloro-4-fluorophenyl or 2,4,6-trimethylphenyl.

5 Other more specific compounds of formula I are those wherein Y is



15

wherein

R_{21} is hydrogen or OR_{26} ; R_{22} and R_{23} are each independently hydrogen, C_1 - C_6 alkyl or (C_3 - C_6 cycloalkyl) $(CH_2)_a$, wherein a is 1 or 2; or R_{22} and R_{23} together with the carbon to which they are attached form C_3 - C_6 cycloalkyl or a C_3 - C_6 heterocyclic ring containing one nitrogen or oxygen, each of which is not adjacent to the carbon to which R_{21} , R_{22} and R_{23} are attached, and optionally one carbonyl; R_{26} is hydrogen, C_1 - C_6 alkyl, (C_3 - C_6 cycloalkyl) $(CH_2)_b$, wherein b is 0, 1 or 2, (C_1 - C_3 alkyl)- $C(O)-$, (C_1 - C_3 alkyl) SO_2- , or (C_1 - C_3 alkyl) $_2NC(O)-$; and R_{24} and R_{25} are each independently hydrogen, C_1 - C_6 alkyl, (C_1 - C_6 cycloalkyl)- $(CH_2)_a$, wherein a is 1 or 2, or C_3 - C_{10} branched alkyl.

25 Other more specific compounds of formula I include those wherein X_1R_3 is ethyl or methylthio, those wherein R_1 is (C_1 - C_6) alkyl, and those wherein Z is NR_7R_8 and R_7 is phenyl or phenyl substituted by one of fluoro, chloro, nitro, methyl or methoxy and R_8 is as defined above, preferably, $(CH_2)_3OH$, CH_2CH_2OH or methyl.

Specific, preferred compounds of formula I include 3-methoxymethyl-2-[3-methyl-5-methylthio-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinoline; (3R)-3-methoxymethyl-2-[3-methyl-5-methylthio-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinoline; 3-methoxymethyl-2-[3-methyl-5-methylthio-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-

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pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinoline; {2-[3-methyl-5-methylthio-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol; {2-[3-methyl-5-methylthio-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol; 2-{1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-naphthalene-2-yloxy}-ethanol; 2-{8-[1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-quinolin-7-yloxy}-ethanol; 2-[3,5-diethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline; 1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-4-(2-methoxynaphthalen-1-ylmethyl)-1H-pyrazole; 2-{2-[1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydro-isoquinolin-3-ylmethoxy}-ethanol; 2-{1-[3,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-naphthalen-2-yloxy}-ethanol; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline; and 2-{2-[3,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydro-isoquinolin-3-ylmethoxy}-ethanol.

Specific, preferred compounds of formula I further include 2-[1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline, 2-[3,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline, 2-[1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline, and 2-[3,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline.

The most preferred compounds of formula I include 1-(4-bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H-pyrazole; 4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazole; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[3,5-diethyl-1-(4-ethyl-2,6-dimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[1-(2,6-dimethyl-4-propylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-{4-[4-

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(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-propan-2-ol; 2-{3,5-diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazol-4-ylmethyl}-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-{3,5-diethyl-1-[4-(1-methoxyethyl)-2,6-dimethylphenyl]-1H-pyrazol-4-ylmethyl}-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 1-{4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-propan-1-ol; 3-ethoxymethyl-2-{1-[4-(1-ethoxypropyl)-2,6-dimethylphenyl]-3,5-diethyl-1H-pyrazol-4-ylmethyl}-1,2,3,4-tetrahydro-isoquinoline; and 3-{4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethylpyrazol-1-yl]-3,5-dimethylphenyl}-pentan-3-ol, all tetrahydroisoquinoline-substituted derivatives of which are derived from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline in regard to the optical site; and (R)-2-[1-(4-bromo-2,6-dimethylphenyl)-3-ethyl-5-methanesulfonyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline.

The invention includes a compound of the formula IA (not shown) and the pharmaceutically acceptable acid addition salt thereof. The compounds of the formula IA are identical to those of formula I except that A is $\text{CH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, $\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_3\text{-C}_8 \text{ alkenyl})_2$, or $\text{CH}(\text{CH}_2)_n(\text{C}_3\text{-C}_8 \text{ alkenyl})$ wherein n is 0 to 4.

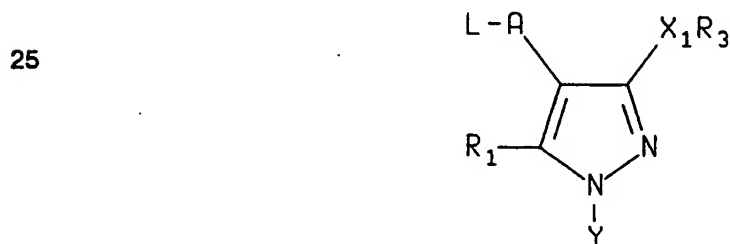
The invention also relates to a pharmaceutical composition for the treatment of (a) illnesses induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as rheumatoid arthritis, pain, asthma, psoriasis and allergies; anxiety disorders, including generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, and post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders, such as depression including major depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; disorders of the immune system including immune dysfunction and human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic syndrome hormone (ADH); and fertility problems, which comprises a compound of the formula I as defined above in an amount effective in the treatment of said illnesses or disorders, and a

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pharmaceutically acceptable carrier. Preferred compositions of the invention are those containing preferred compounds of formula I as described above.

The invention further relates to a method for the treatment of illnesses induced or facilitated by corticotropin releasing factor by administering to a subject in need of
 5 such treatment a compound of formula I as defined above in an amount effective in such treatment, and a method for the treatment of inflammatory disorders such as rheumatoid arthritis, pain, asthma, psoriasis and allergies; anxiety disorders, including
 10 generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, and post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders, such as depression including major depression, and
 15 postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; disorders of the immune system including immune dysfunction and human immunodeficiency virus (HIV) infections; neurodegenerative
 20 diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic syndrome hormone (ADH); and fertility problems, by administering to a subject in need of such treatment a compound
 of formula I as defined above in an amount effective in such treatment. Preferred methods of the invention are those administering a preferred compound of the formula I as described above.

The invention also relates to an intermediate compound of the formula



wherein A is CH₂, R₁ is as defined above with reference to formula I, R₃ is linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₈ alkenyl wherein the double bond is not adjacent to the N or X₁ when X₁ is oxygen or sulfur, C₃-C₇ cycloalkyl (CH₂)_n wherein n is 0, 1, 2, 3

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or 4; or $(CH_2)_q Q_1 R_6$ wherein q is 0, 1 or 2, Q_1 is O, S, NH, $N(C_1-C_6 \text{ alkyl})$ or a covalent bond, and R_6 is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl $(CH_2)_n$ wherein n is 0 to 4, with the proviso that when q is 1, then X_1 and Q_1 can not both be a heteroatom;

5 X_1 is a covalent bond, CH_2NR , wherein R is hydrogen or linear C_1-C_6 alkyl, O, or S;

Y is phenyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or piperidinyl, each of which may be substituted by one to three of any one of fluoro, chloro, bromo, or methyl, or one of trifluoromethyl, provided that Y is not unsubstituted phenyl, and

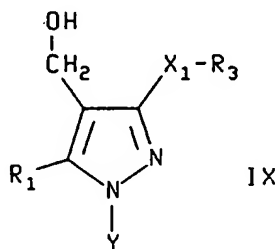
10 L is chloro, bromo, iodo, hydroxy, $O(C=O)(C_1-C_6 \text{ alkyl})$, $OSO_2(C_1-C_6 \text{ alkyl})$, $OSO_2\text{aryl}$ wherein said aryl is phenyl which may be substituted by one to three of fluoro, chloro, bromo, hydroxy, $O(C_1-C_6 \text{ alkyl})$, SH, $S(C_1-C_6 \text{ alkyl})$, amino, $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, or one of iodo, nitro or cyano.

Detailed Description of the Invention

Whenever reference herein is made to the groups $(CH_2)_q Q_1 R_6$ and $(CH_2)_r X_2 (CH_2)_s Q_2 R_6$, then X_1 and Q_1 , and X_2 and Q_2 , respectively, are not both a heteroatom when q or r , respectively, is 1.

Whenever R_1 or Y is a heterocyclic group, the attachment of the group is through a carbon atom.

The compounds of formula I may be prepared by reaction of a compound of the formula

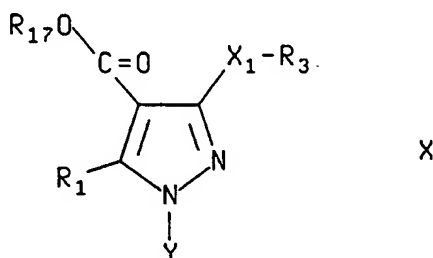


wherein R_1 , X_1 and Y are as defined above with reference to formula I, with a compound of the formula ZH wherein Z is as defined above.

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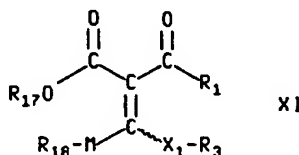
This reaction generally proceeds at temperatures ranging from about 0° to 85°C, usually at room temperature. The reaction is conveniently carried out in a solvent which is inert under the reaction conditions, e.g. acetonitrile. The compound of formula IX is first reacted with an activated sulfonic acid such as methanesulfonyl chloride in the presence of an acid neutralizing agent such as triethylamine in an inert solvent such as methylene chloride at about -10° to about 50°C, before reaction with ZH.

The compounds of formula IX may be prepared by reacting a compound of the formula



wherein R_1 , X_1 and Y are as defined with reference to formula I and R_{17} is C_1 - C_6 alkyl, with a reducing agent such as diisobutylaluminum hydride at temperatures of about -10° to about 80°C, in a reaction-inert solvent such as tetrahydrofuran or ether.

The compounds of formula X may be prepared by reaction of a compound of the formula



with a compound of the formula $Y-NHNH_2$, wherein X_1 , R_1 , R_3 and Y are as defined with reference to formula I except that X_1 is not SO_2 , M is O or S, R_{17} is as defined above with reference to formula X, and R_{18} is C_1 - C_6 alkyl. The reaction is usually carried out in a solvent, such as a C_1 - C_6 alcohol, at least 50 to 150°C, conveniently the reflux temperature of the reaction mixture. The wavy line \sim in formula XI indicates that

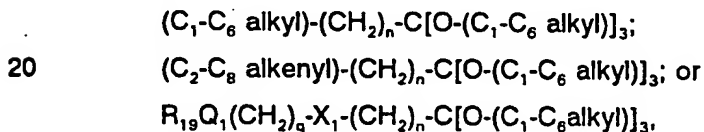
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either isomer of this compound is included, in accordance with accepted conventions for indicating stereoisomers.

The compounds of formula X wherein R_1 is $\text{SO}_2(\text{C}_1\text{-C}_6 \text{ alkyl})$ may be prepared from the corresponding compounds of formula X wherein R_1 is $\text{S}(\text{C}_1\text{-C}_6 \text{ alkyl})$ by
 5 treatment with an oxidizing agent such as meta-chloroperoxybenzoic acid under reaction conditions which are well known.

The compounds of formula XI above may be prepared by reacting an appropriate beta-ketoester with a base such as sodium hydride in the presence of carbon disulfide in an appropriate solvent or mixture of solvents such as
 10 dimethylsulfoxide or dimethylformamide at a temperature of about -10° to about 40°C followed by quenching of the resulting dianion with an appropriate alkylating agent such as methyl iodide resulting in a 3,3-bismethylthioacrylate derivative XI wherein R_{18} is R_3 is CH_3 and M is X_1 is S. Reaction of compounds of the formula XI wherein M is X_1 is S and R_3 is R_{18} is $\text{C}_1\text{-C}_6 \text{ alkyl}$ with alcohols $R_3\text{OH}$ in the presence of base then results
 15 in the preparation of the corresponding compounds XI wherein R_{18} is R_3 and M is X_1 is O.

Reaction of an appropriate beta-ketoester with an ortho ester of one of the following formulas:



wherein n , R_{19} , Q_1 , q , and X_1 are as defined with reference to formula I except that X_1 is not SO_2 , in an appropriate solvent such as ethyl acetate at temperatures of about 0° to about 100°C results in compounds of the formula XI wherein R_{18} is $\text{C}_1\text{-C}_6 \text{ alkyl}$, M
 25 is O, X_1 is CH_2 or a covalent bond, and R_3 is, respectively, $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{-(CH}_2\text{)}_n$; $(\text{C}_2\text{-C}_8 \text{ alkenyl})\text{-(CH}_2\text{)}_n$; and $\text{R}_{19}\text{Q}_1(\text{CH}_2)_q\text{-X}_1\text{-(CH}_2\text{)}_n$, wherein n , q , R_{19} , Q_1 and X_1 are as defined above.

Reaction of the compounds of the formula XI wherein M is X_1 is S and R_3 is R_{18} is $\text{C}_1\text{-C}_6 \text{ alkyl}$ with amines such as RNH_2 or RR_3NH in an appropriate solvent such as
 30 ethanol at temperatures of about 0° to about 100°C results in compounds of the formula XI in which either or both of $R_{18}\text{-M}$ and $X_1\text{-R}_3$ are each RNH or NRR_3 , wherein R is as defined with reference to formula I and R_3 is linear alkyl, branched $\text{C}_3\text{-C}_8 \text{ alkyl}$, or $\text{C}_3\text{-C}_8 \text{ alkenyl}$ wherein the double bond is not adjacent to the nitrogen.

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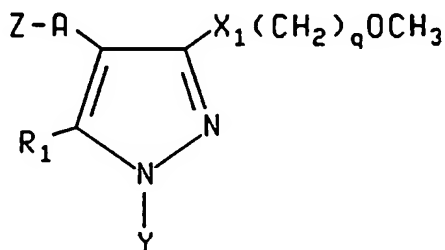
The compounds of formula I wherein Z is as defined above in paragraphs (a), (h) or (i) wherein R_5 or R_{14} is $X_2(CH_2)_rQ_2R_6$, wherein Q_2 is oxygen, and X_2 , r , and R_6 are as previously defined except that R_6 is not hydrogen, may be prepared by alkylation of the corresponding compound wherein R_5 or R_{14} are $(CH_2)_r-X_2-(CH_2)_2-Q_2-R_6$ and $-X_2-(CH_2)_rQ_2R_6$, respectively, wherein R_6 is hydrogen and Q_2 is oxygen. In these cases wherein R_5 and R_{14} have a terminal hydroxy group, the hydroxy is first reacted with a strong base such as an alkali metal hydride, e.g. lithium, sodium or potassium hydride, in a solvent such as dimethylformamide at about 50° to 100°C.

The resulting alkali metal alkoxide is then reacted with an alkyl or aryl sulfonyl ester of the formula $HO(CH_2)_rQ_2R_6$ wherein R_6 is as defined in paragraph (a) except hydrogen. This reaction is carried out in the presence of a solvent such as methylene chloride or toluene at about 50° to 100°C. The above sulfonyl esters may be prepared by the same method as described above for the activation of the compound of formula IX.

The above alkali metal hydride may be replaced by other strong bases including organometallic bases such as n-butyl lithium or amine anion bases such as lithium diisopropylamide. In such case, the metal alkoxide formation reaction may be carried out in tetrahydrofuran at temperatures of about -5° to about 65°C.

The same alkylation may be used to prepare compounds of the formula I wherein X_1 is oxygen and R_3 is $(CH_2)_qQ_1R_{19}$ wherein q , Q_1 and R_{19} are as defined above with reference to formula I except that R_{19} is not hydroxy, from the corresponding compounds wherein X_1R_3 is hydroxy.

The compounds of the formula IX wherein R_3 is $(CH_2)_qQ_1R_6$ wherein q is as defined with reference to formula I, Q_1 is O and R_6 is methyl, react with ZH, as described above, to form compounds of the formula

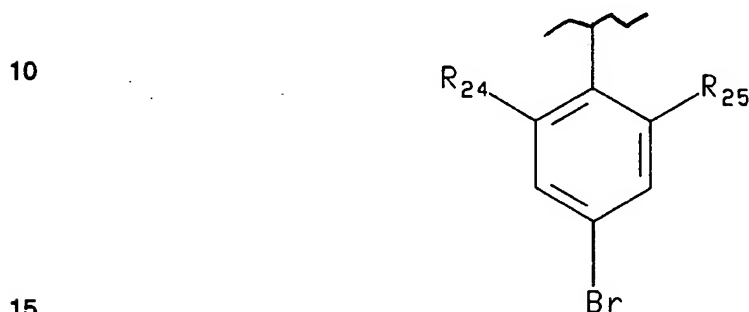


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These compounds may be reacted with a demethylating agent to form the corresponding compound wherein R_6 is hydrogen. A suitable demethylating agent is boron tribromide in combination with sodium iodide and 15-crown-5, as described in the prior art. As explained above, the compound of formula IX is first activated with an
 5 activated sulfonic acid in the presence of an acid neutralizing agent.

An alternative method for making certain compounds of the formula I wherein Y is of the formula XVIII utilizes the starting material of the formula I wherein Y is of the formula

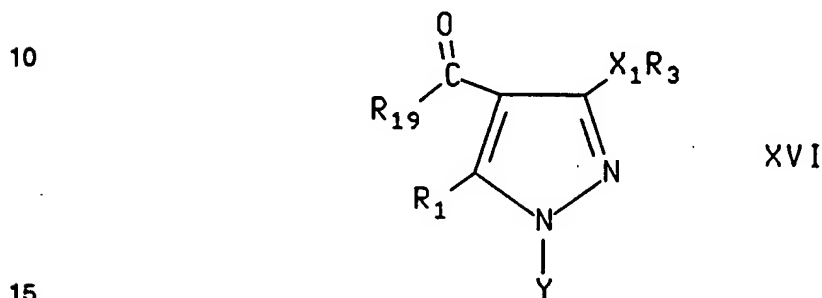


The starting material is reacted with an organolithium reagent, such as $(C_1-C_6 \text{ alkyl})Li$, specifically n-butyllithium, to form in situ the corresponding lithium compound (the lithium compound) wherein the bromo is replaced by lithium. Simple quenching with
 20 water results in the corresponding compound wherein the lithium is replaced by hydrogen. Reaction of the lithium compound with N,N-dimethylformamide results in replacement of the lithium by a formyl group. Reaction of the lithium compound with an aldehyde or ketone of the formula $R_{22}R_{23}C=O$ wherein R_{22} and R_{23} are as defined with reference to formula XVIII results in a corresponding compound wherein the lithium
 25 is replaced by the group $R_{22}R_{23}C(OH)$. The hydroxyl in the latter group may be converted to OR_{26} , wherein R_{26} is as defined with reference to formula XVIII except for hydrogen, by first reacting with sodium hydride, and then reacting with $R_{26}X_3$ wherein R_{26} is as defined with reference to formula XVIII except for hydrogen, and X_3 is bromo, chloro or iodo. Reaction of the lithium compound with a compound of the formula
 30 $R_{22}R_{23}HCX_3$ wherein X_3 is as defined above, and R_{22} and R_{23} are independently hydrogen, C_1-C_6 alkyl or $(C_3-C_6 \text{ cycloalkyl})(CH_2)_a$ wherein a is 1 or 2; or R_{22} and R_{23} taken together with the carbon to which they are attached form C_3-C_6 cycloalkyl, results

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in corresponding compounds of formula I wherein Y is of formula XVIII, wherein R_{21} is hydrogen, and R_{22} and R_{23} are as defined immediately above.

The compounds of formula IA wherein A is $\text{CH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, or $\text{CH}(\text{CH}_2)_n(\text{C}_3\text{-C}_8 \text{ alkenyl})$ wherein n is 0 to 4 (having formula IB, not shown) may be prepared from the
 5 compounds of formula X by reaction with a Grignard reagent of the formula $\text{R}_{19}\text{MgHal}$ wherein R_{19} is $\text{C}_1\text{-C}_6 \text{ alkyl}$, or $(\text{CH}_2)_n(\text{C}_3\text{-C}_8 \text{ alkenyl})$ wherein n is 0 to 4, in a conventional manner, e.g. in diethyl ether or tetrahydrofuran solvent at about -78° to 50°C , to form a ketone of the formula



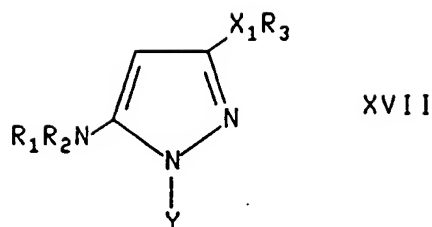
The ketone XVI may be converted to the corresponding enamine by reaction with a compound of the formula ZH wherein Z is (a) to (d) as defined above under standard acid catalyzed dehydration conditions. The enamine may be converted into the
 20 compounds of formula IA wherein A is CHR_{19} by hydrogenation with hydrogen under pressure in the presence of a noble metal catalyst or reduction with a hydride such as sodium or lithium cyanoborohydride in diethylether or tetrahydrofuran (THF).

Alternatively, the compounds of formula IB may be prepared from compounds XVI by reaction with ZH wherein Z is (a) to (d) as defined above in the presence of a
 25 hydride reducing agent such as sodium or lithium cyanoborohydride.

The compounds of formula IA wherein A is $\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or $\text{C}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_3\text{-C}_8 \text{ alkenyl})$ may be prepared from the compound of formula X by reaction with concentrated hydrochloric acid under reflux to form a compound of the formula

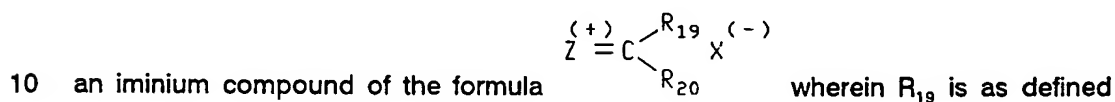
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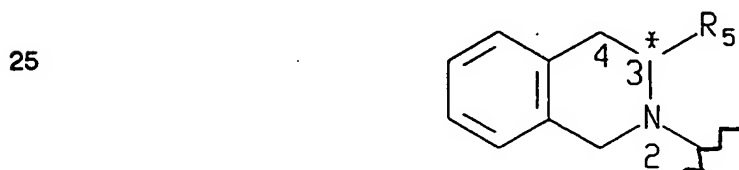
The compound XVII may be brominated, e.g. with pyridinium bromide in THF, to form the corresponding 4-bromide of formula XVIII (not shown) which may be 4-metallated in situ, such as with t-butyl lithium in diethyl ether at -78°C , and then treated in situ with



above, R_{20} is R_{19} , Z is (a) to (d) as defined above, and X is halogen.

The compounds of formula IA wherein A is CHR_{19} , wherein R_{19} is as defined above, Z is (h) or (i) as defined above and R^{14} does not have acidic hydrogens, such as hydroxyls, may be prepared from compounds of the formula I wherein Z is (h) or (i) and the other substituents are as defined above with reference to formula I by treatment with a strong base such as t-butyl lithium in ether or THF and subsequent alkylation in the same solvent with a halide of the formula R_{19}X wherein R_{19} and X are as defined above.

When the compounds of the invention contain a chiral center, it is understood that the invention includes the racemic mixture and the individual enantiomers of such compounds. For instance, the compounds of the invention wherein Z is 1,2,3,4-tetrahydroisoquinolinyl have a chiral center when Z is substituted at position 3 by R_5 , wherein R_5 is as defined with reference to formula I except hydrogen, as follows:

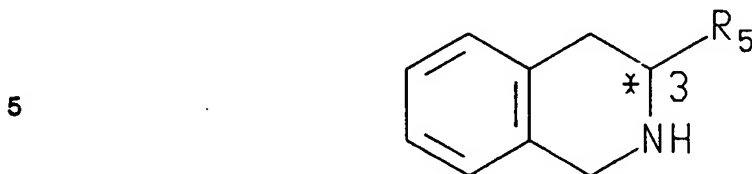


wherein the chiral center is indicated by an asterisk.

30 Preferred compounds of the invention of formula I include those having the R absolute configuration at the 3-site of the 3- R_5 substituted 1,2,3,4-tetrahydroisoquinolyl,

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derived from the dextrorotatory (+) enantiomer of the intermediate compound ZH of the formula



wherein R_5 is hydroxymethyl or (C_1 - C_6 alkoxy) methyl.

The acid addition salts are prepared in a conventional manner by treating a
10 solution or suspension of the free base of formula I or IA with one chemical equivalent
of a pharmaceutically acceptable acid. Conventional concentration or crystallization
techniques are employed in isolating the salts. Illustrative of suitable acids are acetic,
lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric,
sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids
15 such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The novel compounds of the invention of formula I or IA may be administered
alone or in combination with pharmaceutically acceptable carriers, in either single or
multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers,
sterile aqueous solution and various organic solvents. The pharmaceutical
20 compositions formed by combining the novel compounds of formula I or IA and the
pharmaceutically acceptable carriers are then readily administered in a variety of
dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the
like. These pharmaceutical compositions can, if desired, contain additional ingredients
such as flavorings, binders, excipients and the like. Thus, for purposes of oral
25 administration, tablets containing various excipients such as sodium citrate, calcium
carbonate and calcium phosphate may be employed along with various disintegrants
such as starch, alginic acid and certain complex silicates, together with binding agents
such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating
agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for
30 tableting purposes. Solid compositions of a similar type may also be employed as
fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose
or milk sugar and high molecular weight polyethylene glycols. When aqueous
suspensions or elixirs are desired for oral administration, the essential active ingredient

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therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the novel compound of formula I in
5 sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily
10 available by standard techniques known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

15 The effective dosage for the compound of formula I or IA depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. The daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. For the treatment of inflammatory diseases
20 about 0.1 to about 100 mg/kg will be needed in general, for gastrointestinal diseases about 0.1 to about 50 mg/kg, as well as for anorexia nervosa, hemorrhagic stress, treatment of drug and alcohol withdrawal symptoms and treatment of fertility problems. The daily dosage may be given in a single dose or up to three divided doses.

The methods for testing the compounds of formula I or IA for their CRF
25 antagonist activity are as described in Endocrinology, 116, 1653-1659 (1985) and Peptides 10, 179-188 (1989) which determine the binding activity of a test compound to a CRF receptor. The binding activity for the compounds of formula I generally ranges from about 0.2 nanomolar to about 10 micromolar.

The following Examples illustrate the invention. The designation Et means ethyl.

30

Example I

A. Ethyl 3,3-bismethylthio-2-acetylacrylate.

A solution of 6.50 g (50.0 mmol) of ethyl acetoacetate and 4.18 g (3.30 mL, 55.0 mmol) of carbon disulfide in 60 mL of dry dimethylsulfoxide in a flame-dried 300 mL

flask was treated portionwise at 16 - 18°C with 2.64 g (110 mmol) of oil-free sodium hydride. An additional 100 mL of dimethylsulfoxide was eventually added to facilitate stirring. After the addition was complete, the deep red solution was stirred for 75 minutes and then was quenched with 15.62 g (6.85 mL, 110 mmol) of methyl iodide.

- 5 The reaction mixture was stirred overnight at room temperature. The solution was poured into water and extracted with ether. The extracts were washed with water, dried and evaporated to give a red oil which was used for subsequent reactions without further purification. ¹H-NMR (CDCl₃) δ 1.24 (3H, t, J=7), 2.28 (3H, s), 2.37 (6H, s), 4.21 (2H, q, J=7).

10 B. 4-Ethoxycarbonyl-5-methyl-3-methylthio-1-(2,4,6-trichlorophenyl)pyrazole.

A mixture of 1.22 g (5.23 mmol) of ethyl 3,3-bismethylthio-2-acetylacrylate and 1.11 g (5.23 mmol) of 2,4,6-trichlorophenylhydrazine in 12 mL of ethanol was heated at reflux for 2 hours. The cooled reaction mixture was then poured into cold water and the product was extracted into ether. The ethereal extracts were dried and evaporated

- 15 and the residues were chromatographed on silica gel using 6:1 hexane/ethyl acetate as eluent to give 1.12 g (56%) of the desired product as a crystalline solid, m.p. 95-98°C. ¹H-NMR (CDCl₃) δ 1.38 (3H, t, J=7), 2.30 (3H, s), 2.49 (3H, s.), 4.31 (2H, q, J=7), 7.47 m(2H, s).

20 C. 2-(5-Methyl-3-methylthio-1-(2,4,6-trichlorophenyl)pyrazol-4-yl)methyl-1,2,3,4-tetrahydroisoquinoline.

A solution of 0.340 g (0.89 mmol) of 4-ethoxycarbonyl-5-methyl-3-methylthio-1-(2,3,6-trichlorophenyl)pyrazole in 10 mL of tetrahydrofuran was cooled to 0°C in an ice bath under dry nitrogen and then 2.37 mL of a 1.5 M solution of diisobutylaluminum hydride in toluene (3.56 mmol) was added. The reaction mixture was allowed to warm
25 to room temperature and stir for 2 hours. Then water was added cautiously and the product was extracted into ether which was dried and evaporated to give the product which was used for the subsequent reaction without further purification. ¹H-NMR (CDCl₃) δ 2.07 (3H, s), 2.53 (3H, s), 4.56 (2H, d, J=7), 7.45 (2H, s).

- 30 The above product was dissolved in 10 mL of methylene chloride and 0.62 mL (0.45 g, 4.45 mmol) of triethylamine at 0 - 5°C and treated with 0.21 mL (0.31 g, 2.67 mmol) of methanesulfonyl chloride. After 1 hour at room temperature, the reaction mixture was poured into water and was extracted with ethyl acetate. The solution of product was dried with brine and magnesium sulfate and the solvent was evaporated

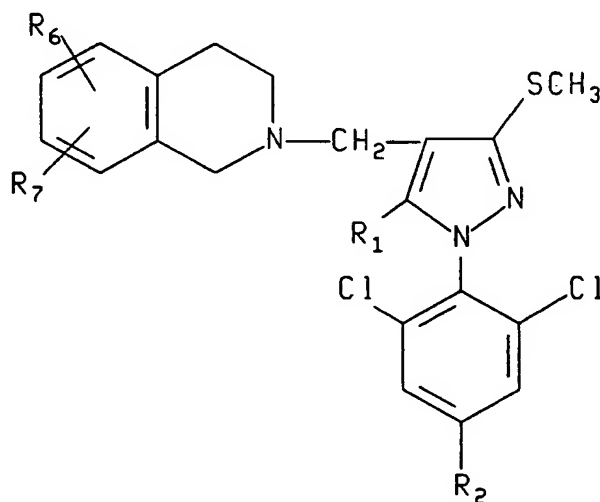
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to give the intermediate mesylate which was used in the subsequent step without further purification.

The product of the above reaction (0.98 mmol) was dissolved in 10 mL of acetonitrile and treated with 0.45 mL (0.475 g, 3.57 mmol) of 1,2,3,4-tetrahydroisoquinoline. The solution darkened and then lightened over a period of a few minutes and was then stirred overnight at room temperature. Solids which had formed were filtered off and discarded and the filtrate was concentrated and chromatographed on silica gel using 4:1 hexane/ethyl acetate as eluent to give the product free base. This material was dissolved in ether and treated with a solution of hydrogen chloride (gas) in ether to give the product hydrochloride, m.p. 205-207°C (53% over the three reactions). Anal. Calcd for $C_{21}H_{20}N_3SCl_3$: C, 51.55; H, 4.33; N, 8.59. Found, C, 51.01; H, 4.69; N, 8.40.

Example 2

The following compounds were prepared by the process of Example 1.



R_1	R_2	R_6	R_7	Physical data (m.p. in °C)
CH_3	Cl	H	H	m.p. 205-207
$CH(CH_3)_2$	Cl	H	H	m.p. 209-210
$CH(CH_3)_2$	Cl	OCH_3	OCH_3	m.p. 140-142

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R ₁	R ₂	R ₆	R ₇	Physical data (m.p. in °C)
phenyl	CF ₃	H	H	¹ H-NMR(CDCl ₃) δ 2.59 (s, 3H), 2.74 (2H, t, J=7), 2.89 (2H, t, J=7), 3.54 (2H, s), 3.64 (2H, s), 6.98-7.01 (1H, m), 7.07-7.15 (3H, m), 7.25-7.32 (3H, m), 7.37-7.42 (2H, m), 7.60 (2H, m).

Example 35 A. 4-Methoxycarbonyl-3,5-heptanedione.

A solution of 6.5 g (50 mmol) of methyl propionyl acetate in 100 mL of ether was treated with 1.19 g (50 mmol) of sodium hydride and the mixture was stirred for 2 hours. The mixture was then cooled to 5 °C and 6.93 g (6.51 mL, 75 mmol) of propionyl chloride was added dropwise over 5 minutes. The reaction mixture was stirred overnight at room temperature and then poured into cold water. This mixture was acidified with sulfuric acid and the product was extracted into ether, washed with water and dried. Evaporation gave the desired product, sufficiently pure for use in the following reaction, in 88% yield. ¹H-NMR (CDCl₃) δ 1.08 (6H, t, J=7), 2.58 (4H, q, J=7), 3.66 (1H, s), 3.74 (3H, s).

15 B. Methyl 1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethylpyrazole-4-carboxylate.

A solution of 7.5 g (40 mmol) of the compound of step A and 11.85 g (48 mmol) of 2,6-dichloro-4-trifluoromethylphenyl hydrazine in 50 mL of ethanol was heated at reflux for 8 hours. The ethanol was removed by evaporation and the residues were partitioned between ethyl acetate and dilute hydrogen chloride. The organic extracts were dried and evaporated to give the desired product in 43% yield as a maroon oil. ¹H-NMR (CDCl₃) δ 1.08 (3H, t, J=7), 1.24 (3H, t, J=7), 2.22 (2H, q, J=7), 2.94 (2H, q, J=7), 3.86 (3H, s), 7.46 (2H, s).

25 C. [1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-yl]methanol.

A solution of 8 g (20 mmol) of the compound of step B in 50 mL of tetrahydrofuran (THF) was treated at °C with 44.1 mL of 1.5 M diisobutylaluminum

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hydride in toluene solution over a period of 5 minutes. The reaction was stirred for 2 hours at °C and was then cautiously quenched with water. The product was extracted into ethyl acetate and dried and evaporated to give the title compound in 46% yield.

¹H-NMR (CDCl₃) δ 1.04 (3H, t, J=7), 1.26 (3H, t, J=7), 2.44 (2H, q, J=7), 2.70 (2H, q, J=7), 4.54 (2H, s), 7.66 (2H, s).

D. 1-[3,5-Diethyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]naphthalen-2-ol.

A solution of 303 mg (2.1 mmol) of 2-naphthol in 5 mL of dry ether was treated with 50 mg (2.1 mmol) of sodium hydride and the mixture was stirred for 15 minutes.

A solution of 368 mg (1.0 mmol) of the compound of step C in 5 mL of dry ether and 126 mg (0.174 mL, 1.22 mmol) of triethylamine was cooled to 0°C and treated with 114 mg (0.077 mL, 1.0 mmol) of methanesulfonyl chloride. Triethylamine hydrochloride was removed by filtration and the filtrate was added to the above suspension of sodium 2-naphthoxide and the reaction mixture was stirred at room temperature for 12 hours.

The reaction mixture was then partitioned between water and ether and the organic extracts were dried and evaporated to give the desired product in 29% yield. ¹H-NMR (CDCl₃) δ 1.00 (3H, t, J=7), 1.20 (3H, t, J=7), 2.44 (2H, q, J=7), 2.72 (2H, q, J=7), 4.58 (2H, s), 6.96 - 7.84 (8H, m).

E. 3,5-Diethyl-4-(2-methoxynaphthalen-1-ylmethyl)-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole.

A solution of 100 mg (0.20 mmol) of the compound at step D in 5 mL of dry THF was treated with 5 mg (0.20 mmol) of sodium hydride and stirred for 15 minutes. Then 85 mg (0.037 mL, 0.60 mmol) of methyl iodide was added and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with water and the product was extracted into ethyl acetate, dried and evaporated. Flash column chromatography gave the desired product as a white solid, m.p. 96 - 98°C. ¹H-NMR (CDCl₃) δ 0.6 (3H, t, J=7), 1.04 (3H, t, J=7), 2.06 (2H, q, J=7), 2.51 (2H, q, J=7), 3.90 (3H, s), 4.14 (2H, s), 7.18 - 7.34 (3H, m), 7.58 (2H, s), 7.70 - 7.84 (3H, m).

Example 4

8-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-quinolin-7-ol

By the general method of Example 3D, substituting 7-hydroxyisoquinoline for 2-naphthol, the title compound was prepared [45 mg of an oil, isolated after flash

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chromatography (silica gel, 40 micron mesh; elution with ethylacetate/hexane=1:4 in volume), from reaction utilizing 264 mg (0.75 mmol) of the compound of Example 3C as starting material. ¹H-NMR(CDCl₃): 0.83 (3H, t), 1.09 (3H, t), 2.37 (2H, q), 2.50 (2H, q), 4.64 (2H, s), 7.14 (1H, d), 7.30 (1H, dd), 7.64 (1H, d), 7.70 (2H, s).

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Example 5

A. 2-{1-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-naphthalen-2-yloxy}-ethanol tert-butyl-dimethylsilylether

To a tetrahydrofuran (1.0 ml) solution of the compound of Example 3D (150 mg, 0.30 mmol), sodium hydride (37 mg of 60% sodium hydride mineral oil dispersion; 22.2 mg, 0.93 mmol of sodium hydride) was added portionwise over several minutes; 1-iodo-2-(tert-butyldimethylsilyloxy)ethane (858 mg, 0.30 mmol) was added, and the reaction was stirred and heated at 45°C for 48 hours. An additional (858 mg, 0.30 mmol) portion of 1-iodo-2-(tert-butyldimethylsilyloxy)ethane was added; and the reaction was then heated at 45°C for an additional 18 hours. The solvent was removed in vacuo, and the residue was extracted into ethyl acetate/water (100 ml of each). The separated aqueous layer was extracted twice with 30 ml portions of ethyl acetate. The combined organic extracts were dried (anhydrous sodium sulfate) and concentrated in vacuo to an oil (1.95 g). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexane=5:95 in volume) afforded the title compound (40 mg) as an oil. ¹H-NMR(CDCl₃): 0.10(6H, s), 0.60 (3H, t), 0.90 (9H, s), 1.10 (3H, t), 2.10 (2H, q), 2.56 (2H, q), 4.00 (2H, q), 4.20 (2H, q), 4.32 (2H, s), 7.25-7.38 (3H, m), 7.65 (2H, s), 7.73-7.87 (3H, m).

B. 2-{1-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-naphthalen-2-yloxy}-ethanol

A tetrahydrofuran (0.40 ml) solution of the compound of step A, (40 mg, 0.06 mmol) and tetrabutylammonium fluoride (123 μ l of a 1.00 M tetrahydrofuran (THF) solution, 0.123 mmol) was stirred at ambient temperature for 3 hours. The solvent was removed in vacuo, and the residue was extracted into ethyl acetate/water (60 ml of each). The separated organic phase was extracted twice with equal volume portions of water, dried over anhydrous sodium sulfate, and concentrated in vacuo to an oil (49 mg). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethylacetate/hexane=3:7 in volume) afforded the title compound (24 mg) as an amorphous solid. ¹H-NMR(CDCl₃): 0.58(3H,t), 1.15 (3H, t), 1.99 (1H, broad), 2.07 (2H,

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q), 2.58 (2H, q), 3.99 (2H, m), 4.23 (2H, t), 4.32 (2H, s), 7.2-7.45 (3H, overlapping multiplets), 7.66 (2H, s), 7.80 (2H, dd), 7.91 (1H, d).

Example 6

A. {2-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol

A solution of 368 mg (1.0 mmol) of [1-(2,6-dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-yl]methanol in 10 mL of methylene chloride and 0.2 mL (2.5 mmol) of triethylamine was cooled to 0 - 5 °C. To this was added 0.92 mL (1.2 mmol) of methanesulfonyl chloride and the reaction mixture was stirred at 0 - 5 °C for 15 minutes. Then 1 mL of acetonitrile and 1 mL of dimethylformamide was added and the reaction mixture was heated at reflux overnight. The cooled reaction mixture was taken up with water and with ethyl acetate and the organic extracts were dried and evaporated to an orange oil which was purified by flash chromatography to give the desired product in 45% yield. ¹H-NMR (CDCl₃) δ 0.86 (3H, t, J=7), 1.21 (3H, t, J=7), 2.28 (2H, q, J=7), 2.60 (2H, q, J=7), 2.92-3.04 (1H, m), 3.20-3.32 (1H, m), 3.50-3.90 (7H, m), 6.90-7.24 (4H, m), 7.68 (2H, s).

B. 2-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline

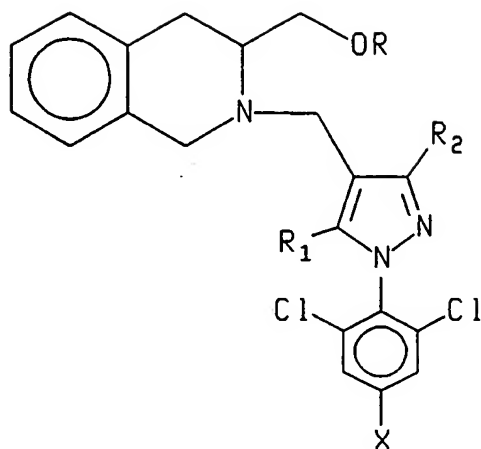
A solution of 200 mg (0.39 mmol) of the compound of step A in 5 mL of THF was treated with 10 mg (0.42 mmol) of sodium hydride and stirred for 30 minutes at room temperature. Then 0.1 mL (1.6 mmol) of methyl iodide was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction was quenched with water and the product was extracted into ethyl acetate which was dried and evaporated. The crude product was flash chromatographed on silica gel to give the desired product in 26% yield as a colorless oil. ¹H-NMR (CDCl₃) δ 0.90 (3H, t, J=7), 1.20 (3H, t, J=7), 2.39 (2H, q, J=7), 2.65 (2H, q, J=7), 2.88-2.96 (1H, m), 3.16-3.20 (1H, m), 3.32 (3H, s), 3.55-3.78 (7H, m), 6.90-7.24 (4H, m), 7.65 (2H, s).

Example 7

The following compounds were prepared according to the process of Example

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	R	R ₁	R ₂	X	¹ H-NMR
Racemate	H	CH ₃	SCH ₃	Cl	(CDCl ₃) δ 1.84 (3H, s), 2.48 (3H, s), 2.88 (2H, d of d, J=7.7), 3.22 (1H, m), 3.40-3.66 (5H, m), 3.79 (1H, d, J=7), 6.88-7.14 (4H, m), 7.40 (2H, s).
Racemate	CH ₃	CH ₃	SCH ₃	Cl	(CDCl ₃) δ 1.96 (3H, s), 2.46 (3H, s), 2.80 (1H, ab quartet, J=7.2), 2.82 (1H, ab quartet, J=7.20), 3.6 (1H, m), 3.32 (3H, s), 3.34-3.74 (6H, m), 6.88-7.10 (4H, m), 7.40 (2H, s).
Enantiomer	H	CH ₃	SCH ₃	Cl	(CDCl ₃) δ 1.80 (3H, s), 2.48 (3H, s), 2.88 (2H, d of d, J=7.7), 3.20 (1H, m), 3.40-3.66 (5H, m), 3.79 (1H, d, J=7), 6.88-7.14 (4H, m), 7.40 (2H, s).
Enantiomer	CH ₃	CH ₃	SCH ₃	Cl	(CDCl ₃) δ 1.96 (3H, s), 2.46 (3H, s), 2.80 (1H, ab quartet, J=7.20), 2.82 (1H, ab quartet, J=7.20) 3.16 (1H, m), 3.32 (3H, s), 3.34-3.74, (6H, m), 6.88-7.10 (4H, m), 7.40 (2H, s).

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	R	R ₁	R ₂	X	¹ H-NMR
Racemate	H	CH ₃	SCH ₃	CF ₃	(CDCl ₃) δ 2.06 (3H, s), 2.24 (3H, s), 2.70 (1H, ab quartet, J=7, 30), 2.72 (1H, ab quartet, J=7, 30), 3.20 (1H, m), 3.50-3.80 (6H, m), 6.88-7.12 (4H, m), 7.65 (2H, s).
Racemate	CH ₃	CH ₃	SCH ₃	CF ₃	(CDCl ₃) δ 2.12 (3H, s), 2.32 (3H, s), 2.78 (1H, ab quartet, J=7, 16), 2.80 (1H, ab quartet, J=7, 16), 3.18 (1H, m), 3.30 (3H, s), 3.50-3.90 (6H, m), 6.92-7.16 (4H, m), 7.64 (2H, s).
Racemate	H	Et	Et	Cl	(CDCl ₃) δ 0.84 (3H, t, J=7), 1.22 (3H, t, J=7), 2.28 (2H, q, J=7), 2.60 (2H, q, J=7), 2.56 (1H, d of d, J=7, 15), 3.26 (1H, m), 3.50-3.86 (6H, m), 6.96-7.08 (4H, m), 7.42 (2H, s).
Racemate	CH ₃	Et	Et	Cl	(CDCl ₃) δ 0.92 (3H, t, J=7), 1.20 (3H, t, J=7), 2.38 (2H, q, J=7), 2.66 (2H, q, J=7), 2.80 (1H, ab quartet, J=7, 40), 2.82 (1H, ab quartet, J=7, 40), 3.16 (1H, m), 3.34 (3H, s), 3.35-3.74 (6H, m), 6.92-7.10 (4H, m), 7.40 (2H, s).
5 Enantiomer	H	Et	Et	Cl	(CDCl ₃) δ 0.86 (3H, t, J=7), 1.20 (3H, t, J=7), 2.26 (2H, q, J=7), 2.58 (2H, q, J=7), 2.54 (1H, d of d, J=7, 15), 2.95 (1H, d of d, J=7, 15), 3.24 (1H, m), 3.48-3.84 (6H, m), 6.90-7.08 (4H, m), 7.40 (2H, s).

Example 8

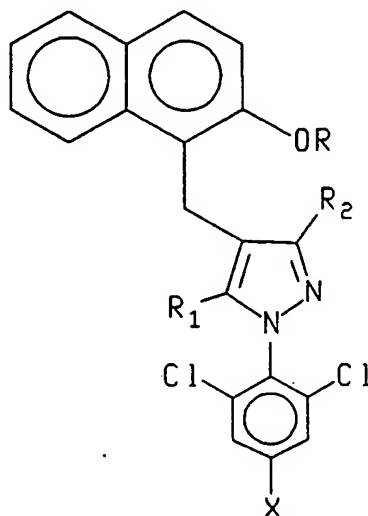
The following compounds were prepared according to Examples 3 and 5.

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R	R ₁	R ₂	X	¹ H-NMR
CH ₃	CH ₃	SCH ₃	Cl	(CDCl ₃) δ 1.48 (3H, s), 2.46 (3H, s), 3.92 (3H, s), 4.14 (2H, s), 7.18-7.38 (3H, m), 7.32 (2H, s), 7.68-7.88 (3H, m).
CH ₃	Et	Et	CF ₃	(CDCl ₃) δ 0.60 (3H, t, J=7), 1.04 (3H, t, J=7), 2.08 (2H, q, J=7), 2.46 (2H, q, J=7), 3.90 (3H, s), 4.26 (2H, s), 7.16-7.34 (3H, m), 7.58 (2H, s), 7.70-7.84 (3H, m).
H	CH ₃	CH ₃	Cl	(CDCl ₃) δ 1.80 (3H, s), 2.10 (3H, s), 4.20 (2H, s), 6.98 (1H, d, J=7), 7.26 (1H, t, J=7), 7.36 (2H, s), 7.37 (1H, t, J=7), 7.55 (1H, d, J=7), 7.72 (1H, d, J=7), 7.78 (1H, d, J=7).
CH ₃	CH ₃	CH ₃	Cl	(CDCl ₃) δ 1.75 (3H, s), 2.06 (3H, s), 3.94 (3H, s), 4.23 (2H, s), 7.21-7.40 (3H, m), 7.40 (2H, s), 7.71-7.86 (3H, m).

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R	R ₁	R ₂	X	¹ H-NMR
CH ₃	Et	Et	CF ₃	(CDCl ₃) δ 0.6 (3H, t, J=7), 2.06 (3H, t, J=7), 2.08 (2H, q, J=7), 2.46 (2H, q, J=7), 3.90 (3H, s), 4.24 (2H, s), 7.18-7.36 (2H, m), 7.60 (2H, s), 7.71 (2H, d, J=8), 7.81 (2H, d, J=8).

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Example 9A. 3,5-Diethyl-1-(2,4,6-trimethylphenyl)pyrazole.

A solution of 7.46 g (0.04 mol) of 2,4,6-trimethylphenylhydrazine hydrochloride, 5.12 g (0.40 mol) of 3,5-heptanedione and 4.18 mL (0.60 mol) of triethylamine in 100 mL of absolute ethanol was refluxed overnight. The solvent was evaporated from the cooled reaction mixture and the residues were partitioned between water and ethyl acetate. The organic extracts were dried with brine and magnesium sulfate, and the solvent was evaporated to give the desired product in 95% yield. This compound was used in the subsequent reaction without further purification ¹H-NMR (CDCl₃): .11 (3H, t, J=7), 1.24 (3H, t, J=7), 1.90 (6H, s), 2.22 (2H, q, J=7), 2.28 (3H, s), 2.65 (2H, q, J=7), 5.96 (1H, s), 6.86 (2H, s).

B. 4-Bromo-3,5-diethyl-1-(2,4,6-trimethylphenyl)pyrazole.

A solution of 6.4 g (0.04 mol) of bromine in 20 mL of glacial acetic acid was added dropwise to a stirred solution of 9.00 g (37 mmol) of 3,5-diethyl-1-(2,4,6-trimethylphenyl)pyrazole in 100 mL of glacial acetic acid. After 1 hour at room temperature, the acetic acid was evaporated under reduced pressure and the residues were dissolved in ethyl acetate. This solution was washed with saturated sodium bicarbonate to remove residual acetic acid, dried with brine and magnesium sulfate, and was concentrated on the rotovap. The product was a tan solid (10.26 g, purification. ¹H-NMR(CDCl₃): 0.92 (3H, t, J=7), 1.15 (3H, t, J=7), 1.86 (6H, s), 2.24 (3H, s), 2.32 (2H, q, J=7), 2.60 (2H, q, J=7), 6.82 (2H, s).

C. 3,5-Diethyl-1-(2,4,6-trimethylphenyl)pyrazole-4-methanol.

A solution of 1.0 g (3.1 mmol) of 4-bromo-3,5-diethyl-1-(2,4,6-trimethylphenyl)pyrazole in 10 mL of anhydrous ether in a flame-dried 3-neck round bottom flask under dry nitrogen with 3.85 mL of 1.7 M t-butyllithium in pentane. After 1 hour, the reaction mixture was treated with 0.355 mL of ethyl chloroformate and was

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then allowed to warm to room temperature. The reaction mixture was quenched with water and then ethyl acetate was added. The aqueous layer was extracted with ethyl acetate again and the organic extracts were combined and dried with brine and magnesium sulfate and then the solvent was removed on the rotovap. This product, 5 3,5-diethyl-4-ethoxycarbonyl-1-(2,4,6-trimethylphenyl)pyrazole, was determined to be 59% pure by gas chromatographic (GC) analysis.

This material, approximately 3.1 mmol, was dissolved in 10 mL of ether and cooled under dry nitrogen to 0°C. Then 7 mL (10 mmol) of 1.5M diisobutylaluminum hydride in toluene was added over about 10 minutes. The reaction mixture was stirred 10 at 0 °C until no starting material was observed by GC and was then quenched with water. The product was extracted into ethyl acetate, dried with brine and magnesium sulfate, and concentrated. The residues were flash chromatographed on silica gel using 4:1 and 1:1 hexane/ethyl acetate as eluent to give the desired product as an oil in the amount of 0.565 g (69% yield for the two reactions). ¹H-NMR (CDCl₃): 0.94 (3H, 15 t, J=7), 1.23 (3H, t, J=7), 1.88 (6H, s), 2.26 (3H, s), 2.35 (2H, 1, J=7), 2.66 (2H, q, J=7), 4.50 (2H, s), 6.82 (2H, s).

D. (R)-{2-[3,5-Diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol.

To a solution of 272 mg (1.0 mmol) of 3,5-diethyl-1-(2,4,6-trimethylphenyl)pyrazole-4-methanol in 5 mL of methylene chloride cooled to 0°C under 20 dry nitrogen in a 25 mL 3-neck flask, was added to 0.2 mL (2.5 mmol) of triethylamine and 0.092 mL (2.0 mmol) of methanesulfonyl chloride. This mixture was stirred for 15 minutes at 0°C and then 0.648 g (4.0 mmol) of (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline in 1 mL of 50:50 dimethylformamide acetonitrile was added. The 25 reaction mixture was heated at reflux overnight whereupon no starting material was seen by TLC. The cooled reaction mixture was diluted with water and the product was extracted with ethyl acetate. After drying (brine wash, magnesium sulfate) and evaporation, the crude product was chromatographed on silica gel, eluting with 10:1 and 5:1 hexane/ethyl acetate to give 184 mg (44%) of the desired product. ¹H-NMR 30 (CDCl₃): 0.80 (3H, t, J=7), 1.18 (3H, t, J=7), 1.92 (6H, s), 2.21 (2H, q, J=7), 2.28 (3H, s), 2.55 (2H, q, J=7), 2.97 (2H, d of d, J=7), 3.25 (1H, m), 3.50 - 3.66 (5H, m), 3.80 (2H, d, J=12), 6.82 - 7.16 (6H, m).

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E. (R)-2-[3,5-Diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydroisoquinoline.

A solution of 150 mg (0.36 mmol) of {2-[3,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol in 5 mL of THF was stirred under dry nitrogen as 11 mg (0.43 mmol) of oil-free sodium hydride was added. The reaction mixture was stirred for 15 minutes and then 0.044 mL (0.72 mmol) of methyl iodide was added. The reaction mixture was stirred overnight and then diluted with water. The product was extracted into ethyl acetate and the organic extracts were dried with brine and magnesium sulfate, and evaporated. The product was isolated pure by chromatography on silica gel using 10:1 and 5:1 hexane/ethyl acetate as eluent to give 84 mg (52%) of a golden oil. ¹H-NMR (CDCl₃): 0.86 (3H, t, J=7), 1.20 (3H, t, J=7), 1.92 (6H, s), 2.28 (3H, s), 2.32 (2H, q, J=7), 2.63 (2H, q, J=7), 2.83 (2H, d of ABq), 3.17 (1H, m), 3.33 (3H, s), 3.34 - 3.38 (1H, m), 3.54 - 3.76 (5H, m), 6.83 - 7.16 (6H, m).

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Example 10

1-(4-Bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazole-4-carboxylic acid methyl ester

A reaction mixture consisting of 3-oxo-2-propionyl-pentanoic acid methyl ester (3.5 g, 0.019 mol), 4-bromo-2,6-dimethylphenylhydrazine (4.75 g, 0.019 mol) and triethylamine (1.8 ml, 0.013 mol) in ethanol (23 ml) was heated at reflux for 5 hours. The ethanol was removed in vacuo and the residue was extracted with methylene chloride/water (15 ml of each). The aqueous phase was separated and twice extracted with equal-volume portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a red-orange oil (7.4 g). Trituration with ethyl acetate (25 ml) afforded a yellow solid which was removed by filtration. Concentration of the filtrate afforded a red-orange oil (6.6 g). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:8 in volume) afforded the title compound (1.1 g) as a light yellow amorphous solid.

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(CDCl₃) δ 1.01 (3H, t), 1.25 (3H, t), 1.94 (6H, s), 2.61 (2H, q), 2.90 (2H, q), 3.86 (3H, s), 7.28 (2H, s).

Example 11[1-(4-Bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-yl]-methanol

To a dry ice/acetone bath-chilled solution of 1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazole-4-carboxylic acid methyl ester (1.1 g, 3.1 mmol) in anhydrous tetrahydrofuran (8 ml), diisobutylaluminum hydride (1.0 M in toluene; 10 ml, 10 mmol) was added dropwise. After 15 minutes, the reaction mixture was warmed to 0°-5°C and stirred at that temperature for 2.5 hours. The reaction was then quenched by addition of 2 ml of water, and the organic solvent was removed in vacuo. Extraction of the residual mixture with ethyl acetate, anhydrous sodium sulfate drying of the resulting extract, and its concentration in vacuo afforded the title compound as a yellow oil (0.77 g).

(CDCl₃) δ 0.99 (3H, t), 1.27 (3H, t), 1.93 (6H, s), 2.38 (2H, q), 2.70 (2H, q), 4.54 (2H, d), 7.28 (2H, s).

Example 12

15 (R)-{2-[1-(4-Bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-yl methyl]-1,2,3,4-tetrahydro-isoquinolin-3-yl}-methanol

To an ice bath-chilled solution of [1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-yl]-methanol (770 mg, 2.3 mmol) and triethylamine (0.382 ml, 2.7 mmol) in methylene chloride (10 ml) methane sulfonyl chloride (0.194 ml, 2.5 mmol) was added dropwise. After stirring the reaction at 0-5°C for 30 minutes, (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (1.49 g, 9.1 mmol) and anhydrous N,N-dimethylformamide (2.2 ml) were added, and the resulting reaction mixture was heated (50°C oil bath) for 21 hours. The solvent was removed in vacuo, and the residue was extracted with ethyl acetate/water (10 ml of each). The aqueous phase was then extracted twice with equal-volume portions of fresh ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a yellow oil (1.5 g). Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:5 in volume) afforded the title compound (0.45 g) as a light yellow oil.

30 (CDCl₃) δ 0.84 (3H, t), 1.22 (3H, t), 1.95 (3H, s), 1.96 (3H, s), 2.25 (2H, q), 2.58 (3H, overlapping 2H, q + 1H, dd), 2.99 (1H, dd), 3.26 (1H, t), 3.61 (5H, m), 3.82 (1H, d), 6.94 (1H, d), 7.13 (3H, m), 7.27 (2H, s).

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Example 13

(R)-2-[1-(4-Bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline

To an ambient temperature solution of (R)-{2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydro-isoquinolin-3-yl}-methanol (0.45g, 0.93 mmol) in anhydrous tetrahydrofuran (12 ml) was added sodium hydride (224 mg of 60% sodium hydride mineral oil dispersion; 5.6 mmol of sodium hydride was added. After stirring for 5 minutes, ethyl iodide (0.37 ml, 4.7 mmol) was added all at once. The reaction mixture was then stirred for 21 hours. The solvent was removed in vacuo, and the remaining residue was extracted with ethyl acetate/water (10 ml of each). The aqueous phase was separated, and then extracted twice with equal volumes of fresh ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a yellow oil (0.67 g). Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:6 in volume) afforded the title compound as a light yellow oil (332 mg).

(CDCl₃) δ 0.86 (3H, t), 1.19 (3H, t), 1.22 (3H, t), 1.94 (6H, s), 2.34 (2H, q), 2.68 (2H, q), 2.76 (1H, dd), 2.94 (1H, dd), 3.20 (1H, m), 3.37 (1H, m), 3.46 (2H, q), 3.67 (5H, m), 6.92 (1H, m), 7.09 (3H, m), 7.24 (2H, s).

Example 14

(R)-2-{4-[4-(3-Ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-propan-2-ol

To a solution of n-butyl lithium (2.5 M hexane solution; 0.16 ml, 0.39 mmol) chilled to -78°C, a solution of (R)-2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline (180mg, 0.35mmol) in anhydrous tetrahydrofuran (1.0 ml) was added dropwise. After stirring at -78°C for 10 minutes, anhydrous acetone (0.078 ml, 1.1 mmol) was added. The resulting mixture was warmed to ambient temperature, and stirred at that temperature for 1 hour. The reaction was quenched by addition of aqueous ammonium chloride (2 ml) and then extracted with ethyl acetate/water (5 ml of each). The separated organic extract was then extracted with an equal volume solution of aqueous ammonium chloride. The combined aqueous extracts were then extracted with a fresh equal-volume portion of ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a yellow oil. Flash chromatography of the

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entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:2 in volume) afforded the title compound (120 mg) as a faint yellow oil.

(CDCl₃) δ 0.88 (3H, t), 1.17 and 1.20 (6H, two overlapping t), 1.52 (6H, s), 1.85 (1H, s), 1.95 (6H, s), 2.33 (2H, q), 2.63 (2H, q), 2.74 (1H, dd), 2.93 (1H, dd), 3.19 (1H, m), 3.36 (1H, m), 3.44 (2H, q), 3.56-3.78 (5H, m), 6.92 (1H, m), 7.08 (3H, m), 7.16 (2H, s).

Example 15

(R)-2-{3,5-Diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazol-4-ylmethyl}-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline

10 To an ambient temperature solution of (R)-2-{4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-propan-2-ol (29 mg, 0.059 mmol) in anhydrous tetrahydrofuran (0.8 ml), sodium hydride (24 mg of 60% sodium hydride mineral oil dispersion; 0.59 mmol of sodium hydride) was added all at once. After 5 minutes of stirring, methyl iodide (0.037 ml, 0.59 mmol) was added, and
15 the resulting reaction mixture was stirred at ambient temperature for 12 hours. The reaction mixture was then extracted with ethyl acetate/water (5 ml of each). The separated aqueous extract was extracted twice with fresh equal-volume portions of ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to a yellow solid (35 mg). Gravity column chromatography (silica
20 gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:2 in volume) afforded the title compound (5 mg) as a yellow oil.

(CDCl₃) δ 0.89 (3H, t), 1.20 and 1.23 (6H, two overlapping t), 1.50 (6H, s), 1.96 (6H, s), 2.37 (2H, q), 2.66 (2H, q), 2.77 (1H, dd), 2.96 (1H, dd), 3.08 (3H, s), 3.22 (1H, m), 3.30-3.90 (8H, overlapping m), 6.94 (1H, m), 7.10 (overlapping 3H m and 2H s).

25

Example 16

(R)-4-[4-(3-Ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethyl-benzaldehyde

To a solution of n-butyl lithium (2.5 M hexane solution; 0.043 ml, 0.11 mmol) chilled to -78°C, a solution of (R)-2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline (50 mg, 0.098 mmol)
30 in anhydrous tetrahydrofuran (0.2 ml) was added dropwise. After stirring at -78°C for 10 minutes, anhydrous N,N-dimethylformamide (0.023 ml, 0.29 mmol) was added. The resulting mixture was warmed to ambient temperature and stirred for 1 hour. The

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reaction quenched by addition of aqueous ammonium chloride (1 ml) and then extracted with ethyl acetate/water (5 ml of each). The separated organic extract was washed with an equal volume solution of aqueous ammonium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a yellow oil (70 mg).

- 5 Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:4 in volume) afforded the title compound (14 mg) as a faint yellow oil.

(CDCl₃) δ 0.87 (3H, t), 1.19 and 1.20 (6H, 2 overlapping t), 2.05 (6H, s), 2.35 (2H, q), 2.67 (2H, q), 2.76 (1H, dd), 2.94 (1H, dd), 3.22 (1H, m), 3.40 (1H, m), 3.47 (2H, q), 3.69-3.90 (5H, m), 6.94 (1H, m), 7.11 (3H, m), 7.63 (2H, s), 9.96 (1H, s).

10

Example 17

(R)-{4-[4-(3-Ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-methanol

- To a solution of (R)-4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl-benzaldehyde (14 mg, 0.030 mmol) in
15 methanol (0.7 ml) at ambient temperature was added sodium borohydride (5 mg, 0.12 mmol). The reaction was stirred for 0.5 hour, then quenched with an aqueous solution of ammonium chloride (1 ml). The mixture was extracted with ethyl acetate/aqueous sodium chloride (2 ml of each). The organic extract was dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (14 mg) as a pure
20 colorless oil.

(CDCl₃) δ 0.85 (3H, t), 1.18 and 1.20 (6H, 2 overlapping t), 1.93 (6H, s), 2.32 (2H, q), 2.65 (2H, q), 2.75 (1H, dd), 2.94 (1H, dd), 3.20 (1H, m), 3.38 (1H, m), 3.46 (2H, q), 3.58-3.80 (5H, m), 4.55 (2H, s), 6.94 (1H, m), 6.98 (2H, s), 7.10 (3H, m).

Example 18

- 25 (R)-2-[3,5-Diethyl-1-(4-ethyl-2,6-dimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline

- To a solution of n-butyl lithium (2.5 M hexane solution; 0.062 ml, 0.16 mmol) chilled to -78°C, a solution of (R)-2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline (72 mg, 0.14 mmol)
30 in anhydrous tetrahydrofuran (0.2 ml) was added dropwise. After stirring at -78°C for 10 minutes, anhydrous ethyl iodide (0.056 ml, 0.70 mmol) was added. The resulting mixture was warmed to ambient temperature and stirred for 1 hour. The reaction was quenched by addition of aqueous ammonium chloride (1 ml), then extracted with ethyl

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acetate/water (5 ml of each). The separated organic extract was washed with an equal volume solution of aqueous ammonium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a yellow oil (46 mg). Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:5 in volume) afforded the title compound (10 mg) as a light yellow oil.

(CDCl₃) δ 0.89 (3H, t), 1.09, 1.20 and 1.12 (9H, 3 overlapping t), 2.94 (6H, s), 2.35 (2H, q), 2.57 (2H, q), 2.65 (2H, q), 2.76 (1H, dd), 2.95 (1H, dd), 3.21 (1H, m), 3.38 (1H, m), 3.46 (2H, q), 3.58-3.79 (5H, m), 6.90 (2H, s), 6.95 (1H, m), 7.10 (3H, m).

Example 19

10 1-[1-(4-Bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-naphthalene-2-ol

A solution of 2-naphthol (2.28 g, 15.8 mmol) in 20 ml of diethylether was treated with sodium hydride (60% mineral oil dispersion, 0.632 g, 15.8 mmol) and the mixture was stirred at ambient temperature for 20 minutes. Methanesulfonyl chloride (0.677 ml, 15 8.7 mmol) was added dropwise to an ice bath cooled solution of [1-(4-bromo-2,6-dimethyl-phenyl)-3,5-diethyl-1H-pyrazol-4-yl]-methanol (2.68 g, 7.9 mmol) and triethylamine (1.38 ml, 9.9 mmol) in diethylether (25 ml). The mixture was stirred at 0°-5°C for 15 minutes; and then stirred at ambient temperature for 20 minutes. The mixture was then added to the above-described sodium 2-naphthoxide suspension. After 20 16 hours stirring at ambient temperature, the reaction mixture was extracted with methylene chloride/dilute aqueous sodium bicarbonate (150 ml and 100 ml, respectively). The aqueous phase was extracted twice with 50 ml portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to an oil (5.65 g). Trituration of the entire sample with ethyl acetate/hexanes (5 ml and 45 ml, respectively) followed by filtration afforded the title compound 1.15 g as a colorless solid.

¹H NMR (CDCl₃): δ 0.67 (t, 3H), 1.16 (t, 3H), 1.95 (s, 6H), 2.16 (q, 2H), 2.59 (q, 2H), 4.31 (s, 2H), 7.02 (d, 1H), 7.26 (s, 2H), 7.33 (t, 1H), 7.44 (t, 1H), 7.66 (d, 1H), 7.78 (d, 1H), 7.95 (d, 1H).

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Example 201-(4-Bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H-pyrazole

Sodium hydride (60% mineral oil dispersion, 0.337 g, 8.4 mmol) was added
5 portionwise to a solution of 1-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-naphthalene-2-ol (1.30 g, 8.4 mmol) in 12 ml anhydrous tetrahydrofuran. After stirring 5 minutes, iodoethane (1.12 ml, 14 mmol) was added, and the resulting reaction mixture was stirred 16 hours at ambient temperature. The solvent was removed in vacuo, and the residue was then extracted with methylene chloride/water (25 ml of
10 each). The aqueous phase was twice extracted with 25 ml portions of fresh methylene chloride. The combined organic extracts were dried (anhydrous sodium sulfate), and concentrated in vacuo to an oily solid (1.92 g). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 6:94 in volume) afforded 1.1 g of the title compound as an off white solid.

15 ¹³C NMR (CDCl₃): 154.1, 153.4, 142.3, 139.2, 137.5, 133.5, 130.8, 129.2, 128.4, 128.1, 125.8, 123.9, 123.2, 122.2, 121.5, 114.2, 114.1, 64.8, 20.2, 19.8, 17.6, 17.2, 15.3, 13.7, 12.9.

Example 212-{4-[4-(2-Ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-propan-2-ol
20

To a solution of n-butyl lithium (0.18 ml of a 2.5 M hexane solution, 0.45 mmol) chilled in a dry ice - acetone bath, a solution of 1-(4-bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H-pyrazole (0.200 g, 0.41 mmol) in 1.0 ml of anhydrous tetrahydrofuran was added dropwise. After stirring for 10 minutes,
25 anhydrous acetone (0.090 ml, 1.23 mmol) was added and the resulting mixture was stirred 10 minutes. The reaction was stirred at ambient temperature for 2 hours before quenching by addition of saturated aqueous ammonium chloride (0.5 ml). The mixture was extracted with ethyl acetate/brine (25 ml of each). The aqueous phase was then extracted twice with 25 ml portions of fresh ethyl acetate. The combined organic
30 extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to an oil (194 mg). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 3:7 in volume) afforded the title compound as a colorless viscous oil (110 mg).

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¹H NMR (CDCl₃) δ 0.56 (3H, t), 1.07 (3H, t), 1.44 (3H, t), 1.51 (6H, s), 1.88 (6H, s), 2.02 (2H, q), 2.51 (2H, q), 4.16 (2H, q), 4.30 (2H, s), 7.11 (2H, s), 7.18-7.36 (3H, m), 7.62-7.78 (2H, m), 7.83 (1H, d).

Example 22

6 4-(2-Ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazole

Sodium hydride (60% mineral oil dispersion, 0.042 g, 1.1 mmol) was added portionwise to a solution of 2-{4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl}-3,5-dimethylphenyl}-propan-2-ol (0.100 g, 0.21 mmol) in anhydrous tetrahydrofuran (THF). After stirring 5 minutes iodomethane (0.132 ml, 2.1 mmol) was added and the resulting mixture was stirred at ambient temperature for 16 hours. The reaction mixture was then extracted with methylene chloride/dilute aqueous sodium bicarbonate (10 ml of each). The aqueous phase was extracted with 10 ml of fresh methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a 150 mg oily residue. Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:4 in volume) afforded the title compound (80 mg) as an amorphous solid.

15 ¹H NMR (CDCl₃) δ 0.60 (3H, t), 1.09 (3H, t), 1.47 (3H, t), 1.50 (6H, s), 1.90 (6H, s), 2.06 (2H, q), 2.54 (2H, q), 3.05 (3H, s), 4.20 (2H, q), 4.32 (2H, s), 7.08 (2H, s), 7.24-7.37 (3H, m), 7.70-7.78 (2H, m), 7.86 (1H, d).

Example 23

4-[4-(2-Ethoxynaphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylbenzaldehyde

A solution of 1-(4-bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H-pyrazole (0.400 g, 0.81 mmol) in 2.0 ml anhydrous THF was added dropwise to a dry ice-acetone bath cooled solution of n-butyl lithium (2.5 M solution in hexane, 0.358 ml, 0.90 mmol). After stirring 10 minutes, anhydrous dimethylformamide (0.188 ml, 2.43 mmol) was added. After 30 minutes the cooling bath was removed and the mixture was stirred 1 hour. The reaction was quenched by addition of 0.25 ml of a saturated aqueous ammonium chloride solution. After stirring for 5 minutes, the reaction mixture was well-mixed with ethyl acetate/brine (20 ml of each). The aqueous phase was then twice extracted with equal-volume portions of fresh ethyl acetate. The combined organic extracts were dried over anhydrous sodium

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sulfate, and concentrated in vacuo to yield an oil (400 mg). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 1:4 in volume) afforded the title compound (100 mg) as an oil.

¹³C NMR (CDCl₃): 191.9, 154.1, 153.8, 143.7, 142.2, 138.4, 136.1, 133.4, 129.3,
5 129.2, 128.4, 128.2, 125.9, 123.8, 123.2, 121.3, 114.4, 114.2, 64.7, 20.3, 19.7, 17.6,
17.4, 15.3, 13.7, 12.9.

Example 24

4-[4-(2-Ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl}-methanol

10 Sodium borohydride (0.127 g, 3.35 mmol) was added to a solution of 4-[4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethyl-benzaldehyde (0.370 g, 8.4 mmol) in 10 ml of methanol. After stirring 30 minutes, the reaction was quenched by addition of 1 ml of brine. The solvent was removed in vacuo, and the residue was extracted with methylene chloride/brine (10 ml of each). The aqueous phase was then
15 twice extracted with 10 ml portions of fresh methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford an oil (490 mg). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 1:1 in volume) yielded the title compound (380 mg) as an oily colorless solid.

20 ¹³C NMR (CDCl₃): 154.1, 153.0, 142.4, 141.7, 136.8, 133.5, 129.2, 128.3, 128.1, 125.8, 124.0, 123.2, 121.6, 114.2, 113.7, 64.8, 64.1, 20.2, 19.8, 17.6, 17.3, 15.3, 13.9, 12.9.

Example 25

1-[4-[4-(2-Ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl]-propan-1-ol

25 A solution of 1-(4-bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H pyrazole (0.200 g, 0.41 mmol) in 1.0 ml of anhydrous tetrahydrofuran was added dropwise to a dry ice-acetone both cooled 2.5 M solution of n-butyl lithium (0.179 ml, 0.45 mmol) in hexane. After stirring the reaction mixture 10
30 minutes, propionaldehyde (0.089 ml, 1.23 mmol) was added. The resulting mixture was stirred 10 minutes, and then removed from the cooling bath and stirred 2 hours. 0.5 ml aqueous saturated ammonium chloride solution was added to quench the reaction. After stirring 10 minutes, the reaction mixture was extracted with methylene

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chloride/brine (10 ml of each). The aqueous phase was then twice extracted with fresh 10 ml portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford an oil (216 mg). Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 3:7 in volume) yielded 133 mg of the title compound as an oil.

¹³C NMR (CDCl₃): 154.1, 152.9, 145.4, 142.4, 137.0, 136.7, 136.6, 133.5, 129.2, 128.4, 128.1, 125.8, 125.7, 125.1, 124.0, 123.2, 121.6, 114.2, 113.7, 64.8, 32.1, 20.2, 19.8, 17.6, 17.4, 17.3, 15.3, 13.9, 12.9, 10.2.

Example 26

10 4-(2-Ethoxy-naphthalen-1-ylmethyl)-1-[4-(1-ethoxy-propyl)-2,6-dimethylphenyl]-3,5-diethyl-1H-pyrazole

Sodium hydride (60% mineral oil dispersion, 0.031 g, 0.78 mmol) was added portionwise to a solution of 1-[4-[4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl]-propan-1-ol (0.123 g, 0.26 mmol) in 0.5 ml anhydrous
15 tetrahydrofuran. After stirring 5 minutes, iodoethane (0.104 ml, 1.3 mmol) was added and the resulting mixture was stirred for 16 hours at ambient temperature. A second portion of sodium hydride (0.031 g of a 60% sodium hydride mineral oil dispersion; 0.78 mmol) was added, followed by a second portion of iodoethane (0.104 ml, 1.3 mmol). After stirring at ambient temperature for 4 hours, the reaction mixture was well-mixed
20 with methylene chloride/aqueous sodium bicarbonate (10 ml of each). The aqueous phase was then twice extracted with 10 ml portions of fresh methylene chloride. The combined organic extracts were then dried over anhydrous sodium sulfate and concentrated in vacuo to afford a 190 mg residue. Flash chromatography of the entire sample (silica gel, 40 micron mesh; elution with ethyl acetate/hexanes = 1:4 in volume)
25 afforded the title compound (45 mg) as an oil.

¹H NMR (CDCl₃): δ 0.57 (t, 3H), 0.84 (t, 3H), 1.08 (t, 3H), 1.14 (t, 3H), 1.46 (t, 3H), 1.68 (m, 2H), 1.87 (s, 3H), 1.88 (s, 3H), 2.03 (q, 2H), 2.52 (q, 2H), 3.30 (m, 2H), 4.05 (t, 1H), 4.19 (q, 2H), 4.32 (s, 2H), 6.94 (s, 2H), 7.28 (m, 3H), 7.74 (m, 2H), 7.84 (d, 1H).

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Example 27(R)-2-[1-(2,6-Dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline

To a solution of n-butyl lithium (2.5 M hexane solution; 0.028 ml, 0.071 mmol) chilled to -78°C, a solution of (R)-2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline (33 mg, 0.065 mmol) in anhydrous tetrahydrofuran (0.1 ml) was added dropwise. After stirring at -78°C for 10 minutes, water (0.1 ml) was added. The resulting mixture was warmed to room temperature and stirred for 20 minutes. The reaction was quenched by addition of aqueous ammonium chloride (1 ml), and then extracted with ethyl acetate/water (5 ml of each). The separated organic extract was washed with an equal volume solution of aqueous ammonium chloride, dried over anhydrous sodium sulfate and concentrated in vacuo to afford a yellow oil (17 mg). Flash chromatography (silica gel, 40 micron mesh; elution with ethyl acetate/hexane = 1:5 in volume) afforded the title compound (2 mg) as a yellow oil.

(CDCl₃) δ 0.87 (3H, t), 1.19 and 1.22 (6H, 2 overlapping t), 1.97 (6H, s), 2.33 (2H, q), 2.65 (2H, q), 2.75 (1H, dd), 2.94 (1H, dd), 3.21 (1H, m), 3.38 (1H, m), 3.46 (2H, q), 3.59-3.78 (5H, m), 6.93 (1H, m), 7.19 (5H, m), 7.26 (1H, d).

Example 28

The following compounds of the formula A were prepared according to the procedures of the previous Examples.

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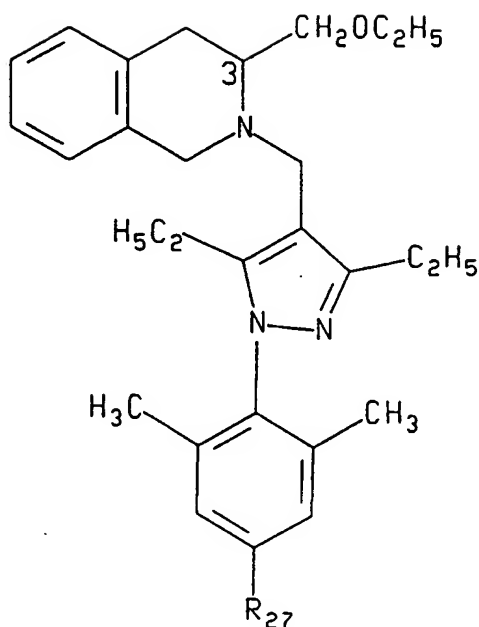
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R_{27}	$^1\text{H-NMR}$
n-propyl	(CDCl_3) δ 0.89 and 0.92 (6H, 2 overlapping t), 1.20 and 1.22 (6H, 2 overlapping t), 1.57 (3H, s), 1.61 (2H, q), 1.95 (3H, s), 2.35 (2H, q), 2.52 (2H, t), 2.66 (2H, q), 2.77 (1H, dd), 2.95 (1H, dd), 3.22 (1H, m), 3.40 (1H, m), 3.47 (2H, q), 3.60-3.80 (5H, m), 6.88 (2H, s), 6.96 (1H, m), 7.11 (3H, m).
n-butyl	(CDCl_3) δ 0.89 and 0.92 (6H, 2 overlapping t), 1.20 and 1.22 (6H, 2 overlapping t), 1.33 (2H, m), 1.57 (2H, m), 1.94 (6H, s), 2.36 (2H, q), 2.55 (2H, t), 2.66 (2H, q), 2.77 (1H, dd), 2.96 (1H, dd), 3.22 (1H, m), 3.40 (1H, m), 3.47 (2H, q), 3.58-3.80 (5H, m), 6.88 (2H, s), 6.95 (1H, m), 7.11 (3H, m).
2-methyl-propyl	(CDCl_3) δ 0.87 and 0.89 (9H, overlapping 6H d and 3H t), 1.19 (6H, 2 overlapping t), 1.30 (1H, m), 1.90 (6H, s), 2.33 (2H, q), 2.38 (1H, m), 2.53 (1H, m), 2.64 (2H, q), 2.75 (1H, dd), 2.94 (1H, dd), 3.20 (1H, m), 3.37 (1H, m), 3.45 (2H, q), 3.56-3.78 (5H, m), 6.82 (1H, s), 6.85 (1H, s), 6.92 (1H, m), 7.08 (3H, m).

R_{27}	$^1\text{H-NMR}$
CH_2OCH_3	(CDCl_3) δ 0.86 (3H, t), 1.19 and 1.21 (6H, 2 overlapping t), 1.97 (6H, s), 2.33 (2H, q), 2.66 (2H, q), 2.76 (1H, dd), 2.94 (1H, dd), 3.20 (1H, m), 3.38 (4H, overlapping 3H, s and 1H, m), 3.46 (2H, q), 3.58-3.78 (5H, m), 4.40 (2H, s), 6.71 (1H, m), 7.05 (2H, s), 7.10 (3H, m).
$\text{C}^*\text{H}(\text{OH})\text{CH}_3^1$	(CDCl_3) δ 0.87 (3H, t), 1.19 and 1.21 (6H, 2 overlapping t), 1.43 (3H, d), 1.95 (3H, s), 1.96 (3H, s), 2.34 (2H, q), 2.42 (1H, m), 2.65 (2H, q), 2.74 (1H, dd), 2.94 (1H, dd), 3.21 (1H, m), 3.39 (1H, m), 3.46 (2H, q), 3.59-3.79 (5H, m), 4.79 (1H, broad q), 6.95 (1H, m), 7.03 (1H, s), 7.07 (4H, overlapping 1H, s and 3H, m).
$\text{C}^*\text{H}(\text{OH})\text{C}_2\text{H}_5^1$	(CDCl_3) δ 0.87 and 0.89 (6H, 2 overlapping t), 1.19 and 1.21 (6H, overlapping t), 1.72 (2H, q), 1.95 (3H, s), 1.96 (3H, s), 2.33 (2H, q), 2.65 (2H, q), 2.75 (1H, dd), 2.94 (1H, dd), 3.20 (1H, m), 3.38 (1H, m), 3.45 (2H, q), 3.58-3.77 (5H, m), 4.49 (1H, t), 6.93 (1H, m), 6.99 (1H, s), 7.05 (1H, s), 7.09 (3H, m).
$\text{C}^*\text{H}(\text{OCH}_3)\text{CH}_3^1$	(CDCl_3) δ 0.89 (3H, t), 1.18 and 1.20 (6H, two overlapping t), 1.40 (3H, d), 1.97 (6H, s), 2.36 (2H, q), 2.65 (2H, q), 2.76 (1H, dd), 2.95 (1H, dd), 3.21 (4H, overlapping 3H, s and 1H, m), 3.38 (1H, m), 3.46 (2H, q), 3.59-3.79 (5H, m), 4.23 (1H, q), 6.95 (1H, m), 7.10 (2H, s), 7.10 (3H, m).
5 $\text{C}^*\text{H}(\text{OC}_2\text{H}_5)\text{C}_2\text{H}_5^1$	(CDCl_3) δ 0.84 and 0.86 (6H, 2 overlapping t), 1.14, 1.18 and 1.20 (9H, 3 overlapping t), 1.60 (2H, m), 1.75 (1H, m), 1.94 (6H, s), 2.33 (2H, q), 2.63 (2H, q), 2.74 (1H, dd), 2.93 (1H, dd), 3.19 (1H, m), 3.28 (2H, q), 3.35 (1H, m), 3.45 (2H, q), 3.58-3.80 (5H, m), 4.02 (1H, t), 6.92 (1H, m), 6.97 (2H, s), 7.08 (3H, m).
$\text{C}(\text{CH}_3)_2\text{OC}_2\text{H}_5$	(CDCl_3) δ 0.87 (3H, t), 1.12 (3H, t), 1.17 and 1.20 (6H overlapping t), 1.49 (6H, s), 1.95 (6H, s), 2.34 (2H, q), 2.63 (2H, q), 2.74 (1H, dd), 2.93 (1H, dd), 3.20 (2H, q), 3.38 (1H, m), 3.45 (2H, q), 3.58-3.78 (5H, m), 7.13 (1H, m), 7.10 (5H, overlapping 2H, s and 3H, m).

R_{27}	$^1\text{H-NMR}$
$\text{C}^*\text{H}(\text{OC}_2\text{H}_5)\text{cyclopropyl}^1$	(CDCl_3) δ 0.13 (1H, m), 0.42 (2H, m), 0.63 (1H, m), 0.90 (3H, t), 1.18, 1.19, 1.22 (9H, 3 overlapping t), 1.98 (6H, s), 2.37 (2H, q), 2.66 (2H, q), 2.77 (1H, dd), 2.96 (1H, dd), 3.22 (1H, m), 3.40 (3H, overlapping 2H, q and 1H, m), 3.56 (2H, q), 3.60-3.80 (7H, overlapping m), 6.96 (1H, m), 7.02 (1H, s), 7.05 (1H, s), 7.12 (3H, m).
$\text{C}(\text{C}_2\text{H}_5)_2\text{OH}$	(CDCl_3) δ 0.75 (6H, t), 0.86 (3H, t), 1.21 (6H, 2 overlapping t), 1.69 (1H, s), 1.80 (4H, m), 1.97 (6H, s), 2.34 (2H, q), 2.66 (2H, q), 2.76 (1H, dd), 2.94 (1H, dd), 3.21 (1H, m), 3.39 (1H, m), 3.46 (2H, q), 3.59-3.79 (5H, m), 6.93 (1H, m), 7.07 (3H, m), 7.10 (2H, s).
$\text{C}(\text{C}_2\text{H}_5)_2\text{OCH}_3$	(CDCl_3) δ 0.70 (6H, t), 0.86 (3H, t), 1.20 and 1.22 (6H, 2 overlapping t), 1.68-2.18 (4H, overlapping m), 1.98 (6H, s), 2.35 (2H, q), 2.68 (2H, q), 2.78 (1H, dd), 2.96 (1H, dd), 3.08 (3H, s), 3.22 (1H, m), 3.37 (1H, m), 3.48 (2H, q), 3.52 (1H, s), 3.60-3.80 (5H, m), 6.96 (1H, m), 7.08 (2H, s), 7.12 (3H, m).

5 ¹ Both S and R configurations are formed at the C*-site.

All compounds of formula A are derived from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline and are of the R configuration at the 3-site within the tetrahydroisoquinoline group.

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Example 29

A. 3,3-Bismethylthio-2-propionylacrylic acid ethyl ester.

A solution of 5.0 g (34.6 mmol) of ethyl propionyl acetate in 100 mL of DMSO in a 250 mL 3-necked round bottom flask (RBF) under an atmosphere of dry N_2 was cooled to about 18°C and then 8.34 mL (138 mmol) of carbon disulfide was added followed by 3.05 g (76.2 mmol) of 60% NaH added portionwise. The resulting solution was stirred at ambient temperature for 2 hours and then 4.74 mL (76.2 mmol) of methyl iodide was added over a 10 minute period. The reaction mixture was stirred overnight at room temperature and then poured over ice. The desired product was extracted into 100 mL of ether. The organic extracts were washed with water one time and then dried over anhydrous sodium sulfate and evaporated to a brown oil which was used for the

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subsequent reaction without further purification. The purity of the product was 93% by GCMS analysis.

B. 1-(4-Bromo-2,6-dimethylphenyl)-3-ethyl-5-methylthio-1H-pyrazole-4-carboxylic acid ethyl ester.

5 A solution of 8.58 g (34.5 mmol) of 3,3-bismethylthio-2-propionylacrylic acid ethyl ester, 8.67 g (34.5 mmol) of 4-bromo-2,6-dimethylphenylhydrazine hydrochloride and 7.31 g (69.0 mmol) of sodium carbonate in 150 mL of ethanol in a 250 mL RBF under an atmosphere of dry N₂ was refluxed over the weekend. The reaction mixture was cooled to room temperature and evaporated to a reddish solid. This material was
10 partitioned between 150 mL of water and 200 mL of methylene chloride (CH₂Cl₂). The organic layer was separated, dried over sodium sulfate and evaporated to a gum which was chromatographed on a silica gel column eluting with CH₂Cl₂ to give 2.6 g of pure product as a yellow oil. ¹H-NMR (CDCl₃) δ 1.26 (3H, t, J=7), 1.40 (3H, t, J=7), 1.94 (6H, s), 2.33 (3H, s), 2.93 (2H, q, J=7), 4.36 (2H, q, J=7), 7.30 (2H, s).

15 C. 1-(4-Bromo-2,6-dimethylphenyl)-3-ethyl-5-methylsulfonyl-1H-pyrazole-4-carboxylic acid ethyl ester.

A solution of 2.6 g (6.56 mmol) of 1-(4-bromo-2,6-dimethylphenyl)-3-ethyl-5-methylthio-1H-pyrazole-4-carboxylic acid ethyl ester in 50 mL of THF in a 125 mL 3-neck RBF was stirred under N₂ and cooled to 17°C. Then 0.826 g (9.80 mmol) of anhydrous
20 sodium bicarbonate was added followed by a solution of 6.79 g (19.6 mmol) of m-chloroperbenzoic acid dissolved in 40 mL of THF. During the addition, the temperature of the reaction mixture was not allowed to rise above 20°C. After 1 hour, an aliquot workup showed that the reaction mixture consisted of about 34% of the desired sulfone and about 66% of the intermediate sulfoxide and after stirring overnight at room
25 temperature, the conversion to sulfone was complete. A solution of 50 mL of 20% sodium bisulfite was then added and the resulting reaction mixture was stirred for 15 minutes. The reaction mixture was diluted with 50 mL of water and the product was extracted into 100 mL of CH₂Cl₂. The organic extracts were washed twice with saturated bicarbonate solution and once with 20% sodium bisulfite solution. The
30 organic layer was dried over sodium sulfate and evaporated to give the desired product (2.91 g) as a gum. ¹H-NMR (CDCl₃) δ 2.28 (3H, t, J=7), 1.42 (3H, t, J=7), 1.97 (6H, s), 2.93 (2H, q, J=7), 3.39 (3H, s), 4.42 (2H, q, J=7), 7.29 (2H, s).

D. [1-(4-Bromo-2,6-dimethylphenyl)-3-ethyl-5-methylsulfonyl-1H-pyrazol-4-yl]methanol.

A solution of 3.0 g (7.0 mmol) of 1-(4-bromo-2,6-dimethylphenyl)-5-ethyl-3-methylsulfonyl-1H-pyrazole-4-carboxylic acid ethyl ester in 25 mL of ether in a 50 mL
5 3-neck RBF was stirred under a N₂ atmosphere while 3.39 mL of a 1M solution of lithium aluminum hydride in ether was added dropwise. The reaction mixture was stirred at room temperature for 2 hours then excess sodium sulfate decahydrate was added. This mixture was stirred over the weekend and then filtered and the resulting solution was evaporated to a yellow gum. The residue was chromatographed on silica
10 gel eluting with 30:1 CH₂Cl₂/CH₃OH to give 1.0 g of the desired product. ¹H-NMR (CDCl₃) δ1.29 (3H, t, J=7), 1.98 (6H, s), 2.76 (2H, q, J=7), 2.83 (1H, t, J=7), 2.98 (3H, s), 4.74 (2H, d, J=7), 7.30 (2H, s).

E. {2-[1-(4-Bromo-2,6-dimethylphenyl)-3-ethyl-5-methylsulfonyl-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol.

15 In a 50 mL 3-neck RBF equipped with magnetic stirring bar, thermometer, dropping funnel and N₂ atmosphere were placed 861 mg (2.23 mmol) of 1-(4-bromo-2,6-dimethylphenyl)-5-ethyl-3-methylsulfonyl 1H pyrazol-4-ylmethanol and 25 mL of CH₂Cl₂. This solution was cooled in an ice bath and 2.92 mL (19.6 mmol) of diazabicycloundecane was added. Then a solution of 862 mg (11.15 mmol) of
20 methanesulfonyl chloride in 5 mL of CH₂Cl₂ was added dropwise and the resulting solution was stirred for 30 minutes at ice bath temperature. The reaction mixture was poured into ice water and 40 mL of CH₂Cl₂ was added. The organic layer was separated and washed twice with cold brine and then dried over sodium sulfate evaporated to a yellow gum.

25 This gum was dissolved in 25 mL of acetonitrile and treated with 399 mg of 3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline and 945 mg (8.92 mmol) of sodium carbonate. The reaction mixture was stirred for 15 minutes at room temperature and was then refluxed at 65°C for 3 hours. The cooled reaction mixture was partitioned between water and CH₂Cl₂ and the aqueous layer was extracted twice with additional
30 CH₂Cl₂. The combined organic layers were dried and evaporated to a yellow gum which chromatographed on silica gel with CH₂Cl₂:CH₃OH 20:1 as eluent to give the desired product as a yellow gum, 660 mg. ¹H-NMR (CDCl₃) δ1.20 (3H, t, J=7), 1.96

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(3H, s), 2.00 (3H, s), 2.54 (2H, q, J=7), 2.70-3.00 (3H, m), 3.13 (3H, s), 3.60-4.00 (6H m), 6.85-7.40 (6H, m).

F. (R)-3-Ethoxymethyl-1,2,3,4-tetrahydroisoquinoline.

To a solution of 500 mg (3.06 mmol) of (+)-3-hydroxymethyl-1,2,3,4-
5 tetrahydroisoquinoline in 10 mL of DMSO was added 122 mg (3.06 mmol) of NaH (60%
in oil) and the mixture was stirred for 45 minutes at room temperature. Then 0.403 mL
(3.06 mmol) of diethylsulfate was added via syringe. Foaming occurred and subsided
in approximately 15 minutes. The reaction mixture was then stirred at room
temperature overnight and poured into water. The product was extracted into ethyl
10 acetate and dried and evaporated to an oil. This was chromatographed on silica gel
to give the desired product as an oil, 190 mg. ¹H-NMR (CDCl₃) δ 1.22 (3H, t, J=7), 2.29
(1H, broad s), 2.55-2.70 (2H, m), 3.09-3.18 (1H, m), 3.41 (1H, t, J=7), 3.50-3.59 (3H,
m), 4.06 (2H, ABq, J=5, 21), 7.00-7.13 (4H, m).

G. (R)-2-[1-(4-Bromo-2,6-dimethylphenyl)-3-ethyl-5-methanesulfonyl-1H-
15 pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline.

In a 50 mL 3-neck RBF equipped with magnetic stirring bar, thermometer,
dropping funnel and N₂ atmosphere were placed 327 mg (0.85 mmol) of 1-(4-bromo-
2,6-dimethylphenyl)-3-ethyl-5-methylsulfonyl-1H-pyrazol-4-yl]methanol and 20 mL of
CH₂Cl₂. This solution was cooled in an ice bath and 1.02 g (6.77 mmol) of
20 diazabicycloundecane was added. Then a solution of 484 mg (4.23 mmol) of
methanesulfonyl chloride in 5 mL of CH₂Cl₂ was added dropwise and the resulting
solution was stirred for 30 minutes at ice bath temperature. The reaction mixture was
poured into ice water 40 mL of CH₂Cl₂ was added. The organic layer was separated
and washed twice with cold brine and then dried over sodium sulfate and evaporated
25 to a yellow gum.

This gum dissolved in 25 mL of acetonitrile and treated with 180 mg (0.94 mmol)
of (R)-3-ethoxymethyl-1,2,3,4-tetrahydroisoquinoline and 359 mg (3.38 mmol) of sodium
carbonate. The reaction mixture was stirred for 15 minutes at room temperature and
was then refluxed at 65°C for 3 hours. The cooled reaction mixture was partitioned
30 between water and CH₂Cl₂ and the aqueous layer was extracted twice with additional
CH₂Cl₂. The combined organic layers were dried and evaporated to a yellow gum
which was chromatographed on silica gel with 40:1 CH₂Cl₂/CH₃OH as eluent to give
292 mg of the desired product as a yellow solid. ¹H-NMR (CDCl₃) δ 1.21 (3H, t, J=7),

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1.27 (3H, t, J=7), 1.95 (6H, s), 2.74 (2H, q, J=7), 2.75-2.77 (1H, m), 2.97 (1H, m), 3.13 (3H, s), 3.25-4.11 (9H, m), 6.97-7.29 (6H, m).

The following examples illustrate the preparation of intermediates.

Preparation 1

5 Racemic (1,2,3,4-Tetrahydro-isoquinolin-3-yl)-methanol [also referred to as (±)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline]

To a well stirred, ice-bath-chilled slurry of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (75 g, 0.351 mol, Aldrich Chemical Co.) in anhydrous methanol (600 ml), sodium methoxide (37.92 g, 0.702 mol) was added in small solid portions over a 10 minute period. After 30 minutes of brisk stirring, the methanol was removed and the colorless residue was dried in vacuo overnight. The entire sample was stirred in anhydrous tetrahydrofuran causing the organic portion to dissolve completely. A 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (351 ml, 0.351 mol) was added in a rapid stream to the well-stirred mixture over a 20 minute period (mild exotherm). The reaction mixture was then vigorously refluxed for 2 hours. At 5°C, the reaction was quenched by cautious addition of 15% aqueous sodium hydroxide. The mixture was filtered, and the filtrate was concentrated in vacuo to a yellow solid. The entire sample was then dissolved in methylene chloride (400 ml) and filtered to remove residual inorganic salts. Solvent removal in vacuo afforded the title compound as an orange solid (47.01 g, 70% yield). TLC R_f (silica gel plates, u.v. detection, methanol/methylene chloride=5:95 in volume): 0.46; ¹³C NMR(CDCl₃): 135.4, 134.1, 129.3, 126.3, 126.1, 125.9, 65.4, 55.0, 47.8, 30.9.

Preparation 2

25 Dextrorotatory enantiomer of (1,2,3,4-tetrahydro-isoquinolin-3-yl)-methanol [also referred to as (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline]

To a solution of (±)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (Preparation 1; 47.01 g, 0.288 mol) in isopropyl alcohol (159 ml), a solution of (S)-(+)-mandelic acid (43.81 g, 0.288 mol) in isopropyl alcohol (159 ml) was added. The resulting solution was allowed to stand at ambient temperature for 48 hours, during which time a heavy orange crystalline mass formed. The isolated crystalline solid (13.06 g) was dissolved in hot isopropyl alcohol (63 ml). After standing for 1 hour at ambient temperature, the newly-formed crystalline solid was isolated by filtration (8.2 g, m.p. 138°C). The recrystallization procedure was repeated twice more, using 63 ml

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and 60 ml volumes of isopropyl alcohol to afford 7.08 g and 6.76 g of crystalline material, respectively. (In each case, the crystallization was allowed to proceed for 2 hours at ambient temperature prior to filtration.) A 138-139°C m.p. was observed after the final crystallization. The entire sample was dissolved in methylene chloride water
5 (300 ml and 100 ml, respectively) with the pH adjusted to 9.5 (potassium carbonate). The phases were separated, and the aqueous portion was extracted with three 50 ml portions of fresh methylene chloride. The combined organic extracts were dried (anhydrous sodium sulfate) and concentrated in vacuo to afford the optically resolved title compound as a colorless amorphous solid (2.02 g, 8.6% yield). $[\alpha]_D^{20} + 103^\circ$
10 ($c=1.83$, CH_2Cl_2); ^{13}C NMR (CDCl_3): identical to that of the racemic compound prepared in Preparation 1.

Preparation 3

Levorotatory enantiomer of (1,2,3,4-Tetrahydro-isoquinolin-3-yl)-methanol [also referred to as (-)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline]

15 Substituting (R)-(-)-mandelic acid for (S)-(+)-mandelic acid in the Preparation 2 procedure (and utilizing 17.9 g of the alcohol-amine prepared in Preparation 1), the levorotary title compound (0.65 g, 7.3% yield) was obtained as a colorless amorphous solid. $[\alpha]_D^{20} - 100.4^\circ$ (CH_2Cl_2 , $c=1.43$; ^1H NMR and ^{13}C NMR (CDCl_3): identical in all respects to those observed for the racemic (Preparation 1) and dextrorotatory
20 (Preparation 2) products.

Preparation 4

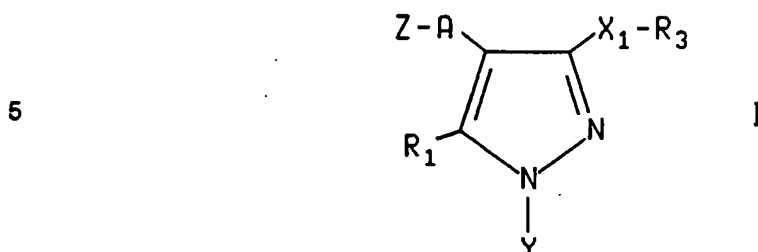
Methyl 3,5-diethyl-1-(2,4,6-trichlorophenyl)pyrazole-4-carboxylate

A mixture of 11.0 g (60.0 mmol) of methyl 2-propionyl-3-ketopentanoate and 11.26 g (65.0 mmol) of 2,4,6-trichlorophenylhydrazine in 50 mL of ethanol was refluxed
25 under nitrogen until disappearance of starting material was noted. The solvent was removed in vacuo and the residues were partitioned between ethyl acetate and dilute hydrogen chloride. The organic layer was dried and evaporated to give the product as an off-white solid which was used for subsequent reactions without further purification. ^1H -NMR: (CDCl_3) δ 1.02 (3H, t, $J=7$), 1.21 (3H, t, $J=7$), 2.62 (2H, q, $J=7$), 2.86 (2H, q, $J=7$), 3.82 (3H, s), 7.42 (2H, s).
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CLAIMS

1. A compound of the formula



- 10 and the pharmaceutically acceptable acid addition salts thereof,
wherein

A is CH₂;

- R₁ is hydrogen; linear or branched C₁-C₆ alkyl; C₃-C₈ alkyl containing one or two
non-adjacent double bonds; hydroxy; O(C₁-C₆ alkyl); SH; S(C₁-C₆ alkyl); SO₂(C₁-C₆
15 alkyl) or C₃-C₆ cycloalkyl; morpholinyl, piperidinyl or aryl which aryl may be substituted
by one to three of fluoro, chloro, bromo, hydroxy, O(C₁-C₆ alkyl), SH, S(C₁-C₆ alkyl),
amino, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, or one of iodo, nitro or cyano, said aryl being
selected from the group consisting of phenyl, thienyl, benzothienyl, pyridyl, quinolyl,
pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl,
20 benzothiazolyl, isothiazolyl, benzoisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl,
pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, or
thiazolidinyl;

- R₃ is linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₈ alkenyl wherein the double
bond is not adjacent to X₁ when X₁ is a heteroatom, C₃-C₇ cycloalkyl(CH₂)_n, wherein n
25 is 0 to 4, or (CH₂)_qQ₁R₁₉, wherein q is 0, 1 or 2, Q₁ is O, S, NH, N(C₁-C₆ alkyl), or a
covalent bond when X₁ is not a covalent bond, and R₁₉ is hydrogen, linear C₁-C₆ alkyl,
branched C₃-C₈ alkyl, C₃-C₈ alkenyl, C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl- (CH₂) with the
proviso that when q is 1, then X₁ and Q₁ cannot both be a heteroatom;

- X₁ is a covalent bond, CH₂, O, S, or NR, wherein R is hydrogen, linear C₁-C₆
30 alkyl or branched C₃-C₈ alkyl;

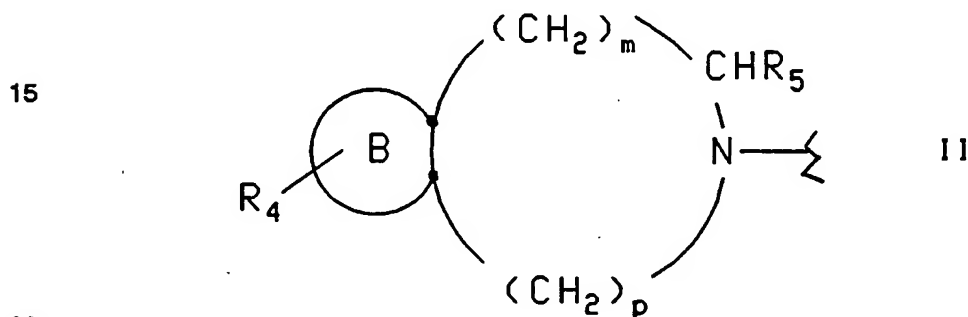
Y is phenyl which is substituted by from one to three of fluoro, chloro, bromo,
formyl, C₁-C₆ alkyl, C₃-C₁₀ branched alkyl, C₁-C₆ alkoxy or trifluoromethyl, or by one of
hydroxy, iodo, cyano, nitro, amino, NH(C₁-C₄ alkyl), N(C₁-C₄)(C₁-C₂ alkyl), COO(C₁-C₄

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alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂,
 NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆
 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C₁-C₄ alkoxy, amino,
 methylamino, dimethylamino or acetyl wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may
 5 contain one double or triple bond; thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl,
 pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl,
 isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl,
 indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or
 piperidinyl, each of which may be substituted by one to three of any one of fluoro,
 10 chloro, bromo, or methyl, or one of trifluoromethyl; and

Z is

(a)



wherein the B ring is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,
 triazolyl, pyrrolyl, pyrazolyl, imidazolyl, thienyl, or indolyl, each of which may be
 substituted by methyl, methoxy, trifluoromethyl, fluoro, chloro, bromo or iodo; or a
 saturated 5- or 6-membered carbocyclic ring or a partially unsaturated ring having one
 25 or two double bonds;

R₄ is hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, fluoro, chloro, bromo, iodo
 or trifluoromethyl;

R₅ is hydrogen, linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₈ alkenyl, or (CH₂)₆-
 X₂-(CH₂)_r-Q₂-R₆;

30 X₂ and Q₂ are each independently O, S, NH, N(C₁-C₆ alkyl), or one of X₂ and Q₂
 may be a covalent bond;

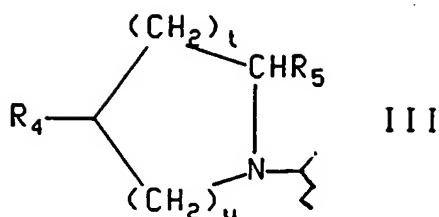
R₆ is hydrogen, linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, or C₃-C₈ alkenyl;

m is 0 or 1;

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o is 1 or 2;
p is 1 or 2; and
r is 0, 1 or 2.

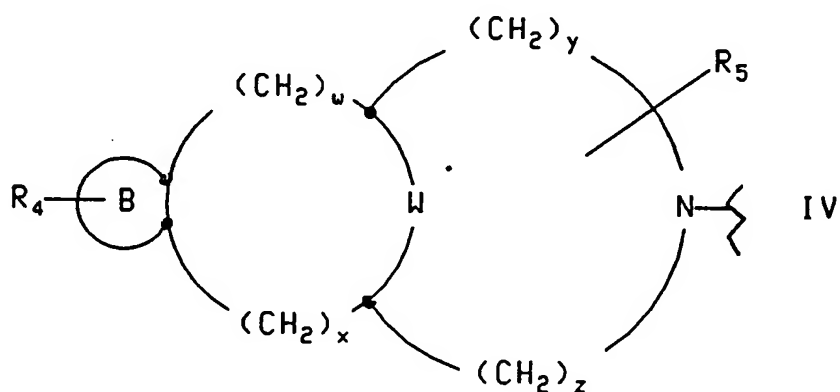
(b)



wherein R_4 and R_5 are as defined above, and t and u are each independently 1 or 2;

(c) $-NR_7R_8$ wherein R_7 and R_8 are each independently hydrogen, C_1 - C_6 linear alkyl, branched C_3 - C_8 alkyl, C_3 - C_8 alkenyl, $(CH_2)_vCH_2OH$, $(CH_2)_vNR_9R_{10}$, wherein v is 0 to 3, and R_9 and R_{10} are each independently hydrogen, or linear C_1 - C_6 alkyl; C_3 - C_{12} cycloalkyl $(CH_2)_n$, C_6 - C_{10} bicycloalkyl $(CH_2)_n$, benzofused C_3 - C_6 cycloalkyl, C_1 - C_6 hydroxyalkyl, phenyl $(CH_2)_n$, each of which may be substituted by one or two of hydroxy, fluoro, chloro, bromo, C_1 - C_5 alkyl, or C_1 - C_5 alkoxy; or R_7 and R_8 may be taken together with the nitrogen to form a saturated or partially unsaturated 5- to 7-membered ring which may contain one of O, S, NH or $N(C_1$ - C_6 alkyl) and which may be substituted by C_1 - C_6 alkyl, hydroxy or phenyl wherein any double bond(s) are not adjacent to any heteroatoms; and n is 0 to 4;

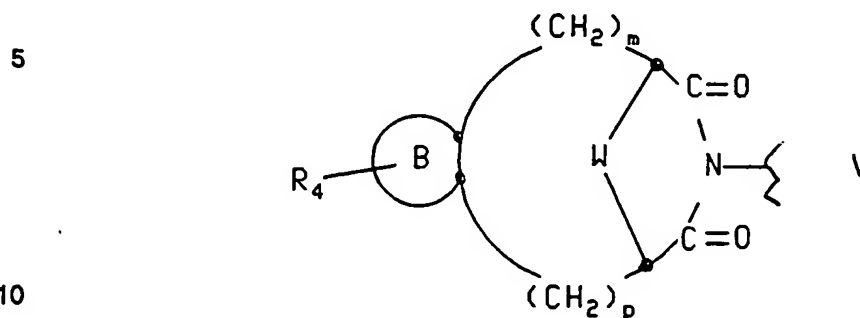
(d)



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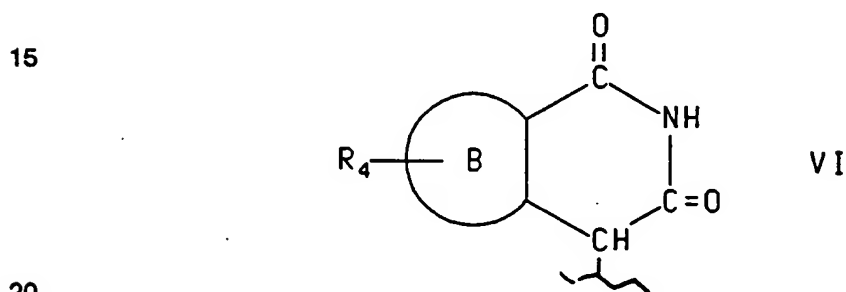
wherein B, W, R_4 and R_5 are as defined above, w, x, y and z are each independently 1 or 2, and W is $(CH_2)_q$ wherein q is as defined above, $N(C_1-C_6 \text{ alkyl})$, or oxygen;

(e)



wherein B, R_4 , m and p are as defined above;

(f)



wherein B and R_4 are as defined above;

(g) $O(CH_2)_v R_{11}$

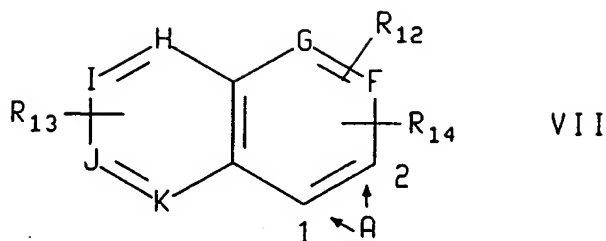
wherein v is 0 to 3 and R_{11} is linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, or thienyl, each of which may be substituted by one or two of any one of fluoro, chloro, bromo, methyl, or trifluoromethyl;

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(h)

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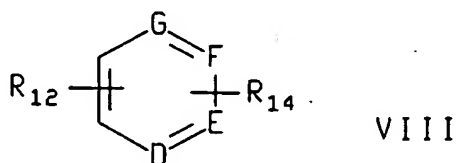


wherein A is defined above and is linked to position 1 or 2 while R_{14} is attached to position 2 or 1, respectively; F, G, H, I, J and K are independently C or N, provided that not more than three of H, I, J and K are N with not more than two adjacent nitrogens; R_{12} and R_{13} each independently are hydrogen, linear C_1 - C_6 alkyl, branched C_3 - C_8 alkyl, C_3 - C_8 alkenyl, fluoro, chloro, bromo, trifluoromethyl, hydroxy, thiol, C_1 - C_{12} alkoxy, C_1 - C_{12} thioalkanyl, or C_3 - C_{12} alkenoxy or C_3 - C_{12} thioalkenyl wherein the double bond is not adjacent to the oxygen; and R_{14} is hydroxy, C_1 - C_{12} alkoxy, C_3 - C_{12} alkenoxy wherein the double bond is not adjacent to the oxygen, or $-X_2-(CH_2)_r-Q_2-R_6$ wherein X_2 , r , Q_2 and R_6 are as defined above in paragraph (a) except that Q_2 is not sulfur, or R_{14} is $NR_{15}R_{16}$ wherein R_{15} and R_{16} are each independently hydrogen, linear C_1 - C_6 alkyl, branched C_3 - C_8 alkyl, C_3 - C_8 alkenyl wherein the double bond is not adjacent to the nitrogen, or C_3 - C_7 cycloalkyl- $(CH_2)_n$ wherein n is as defined above, or R_{15} and R_{16} together with the nitrogen form a saturated five or six membered ring optionally condensed with benzo;

or

(i)

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wherein D, E, F and G are independently C or N, provided that not more than two of D, E, F and G are N, R_{12} and R_{14} are as defined in paragraph (h), A, defined above, is linked to a carbon in formula VIII, and R_{14} is linked to the carbon located adjacent to the carbon to which A is linked.

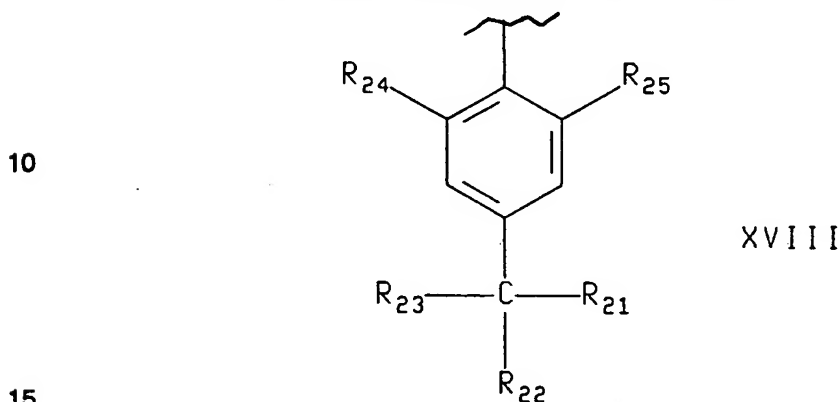
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2. A compound according to claim 1 wherein Y is 2,4,6-tri-substituted phenyl.

3. A compound according to claim 1 wherein Y is 2,4,6-trichlorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 2,6-dibromo-4-fluorophenyl, 2,6-dimethyl-4-bromophenyl, or 2,4,6-trimethylphenyl.

4. A compound according to claim 1 wherein Y is



wherein

R_{21} is hydrogen or R_{26} ;

R_{22} and R_{23} are each independently hydrogen, C_1 - C_6 alkyl or (C_3 - C_6 cycloalkyl) $(CH_2)_a$ wherein a is 1 or 2; or

R_{22} and R_{23} together with the carbon to which they are attached form C_3 - C_6 cycloalkyl or a C_3 - C_6 heterocyclic ring containing one nitrogen or oxygen each of which is not adjacent to the carbon to which R_{21} , R_{22} and R_{23} are attached, and optionally one carbonyl;

R_{26} is hydrogen, C_1 - C_6 alkyl, (C_3 - C_6 cycloalkyl) $(CH_2)_b$ wherein b is 0, 1 or 2, (C_1 - C_3 alkyl)-C(O)-, (C_1 - C_3 alkyl) SO_2 -, or (C_1 - C_3 alkyl) $_2$ NC(O)-; and

R_{24} and R_{25} are each independently hydrogen, C_1 - C_6 alkyl, (C_1 - C_6 cycloalkyl) $(CH_2)_a$ wherein a is 1 or 2, or C_3 - C_{10} branched alkyl.

5. A compound according to claim 1 wherein X_1R_3 is ethyl, methylthio or methylsulfonyl.

6. A compound according to claim 1 wherein R_1 is (C_1 - C_6) alkyl.

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7. A compound according to claim 1 wherein Z is NR_7R_8 wherein R_7 is phenyl or phenyl substituted by one of fluoro, chloro, trifluoromethyl, nitro, methyl or methoxy.

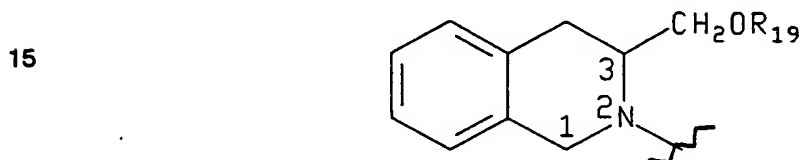
8. A compound according to claim 7 wherein R_8 is $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$,
5 $\text{CH}_2\text{CH}_2\text{OH}$, or methyl.

9. A compound according to claim 1 wherein Z is 1,2,3,4-tetrahydroisoquinolin-2-yl substituted by R_5 which is $(\text{CH}_2)_6\text{-X}_2\text{-(CH}_2)_7\text{-Q}_2\text{-R}_6$.

10. A compound according to claim 9 wherein R_5 is $(\text{CH}_2)_k\text{OH}$ wherein k is 1 to 4, or $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OR}_6$.

11. A compound according to claim 1 wherein Z is 1, 2, 3, 4-tetrahydroisoquinolin-2-yl, wherein R_5 is substituted at position 3, and the absolute configuration at the 3-position is S or R or R,S.

12. A compound according to claim 1 wherein Z is of the formula



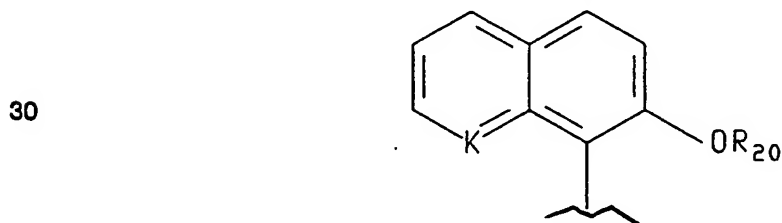
with the absolute configuration at position 3 determined by its derivation from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline, wherein R_{19} is methyl, ethyl, isopropyl,
20 cyclopropylmethylene, or 2-hydroxyethyl.

13. A compound according to claim 1 wherein Z is as defined in (h).

14. A compound according to claim 12 wherein A is linked to position 1, R_{14} is at position 2 and is $\text{X}_2\text{-(CH}_2)_7\text{-Q}_2\text{-R}_6$.

15. A compound according to claim 14 wherein F, G, H, I, and J are each
25 carbon, K is carbon or nitrogen, and R_{14} is 2-methoxy, 2-ethoxy, 2-isopropoxy, or 2-cyclopropylmethoxy.

16. A compound according to claim 1 wherein Z is

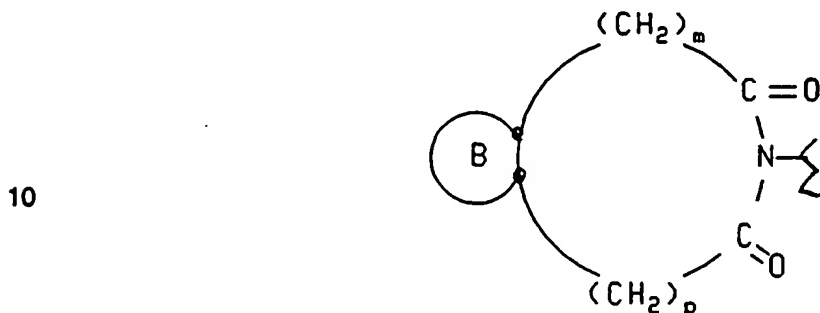


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wherein K is C or N and R_{20} is methyl, ethyl, isopropyl, cyclopropylmethylene, methoxyethylene or hydroxyethylene.

17. A compound according to claim 1 wherein Z is as defined in (a), B is phenyl, p and m are each 1, and R_5 is CH_2OCH_3 or $\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$.

5 18. A compound according to claim 1 wherein Z is



wherein B is phenyl, m is 0, and p is 1.

15 19. A compound according to claim 1 which is 1-(4-bromo-2,6-dimethylphenyl)-4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1H-pyrazole; 4-(2-ethoxy-naphthalen-1-ylmethyl)-3,5-diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazole; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-methoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[1-(4-bromo-2,6-dimethylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[3,5-diethyl-1-(4-ethyl-2,6-dimethylphenyl)-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[1-(2,6-dimethyl-4-propylphenyl)-3,5-diethyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl]-propan-2-ol; 2-[3,5-diethyl-1-[4-(1-methoxy-1-methylethyl)-2,6-dimethylphenyl]-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 2-[3,5-diethyl-1-[4-(1-methoxyethyl)-2,6-dimethylphenyl]-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-tetrahydro-isoquinoline; 1-[4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethyl-pyrazol-1-yl]-3,5-dimethylphenyl]-propan-1-ol; 3-ethoxymethyl-2-[1-[4-(1-ethoxypropyl)-2,6-dimethylphenyl]-3,5-diethyl-1H-pyrazol-4-ylmethyl]-1,2,3,4-tetrahydro-isoquinoline; 3-[4-[4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-3,5-diethylpyrazol-1-yl]-3,5-dimethylphenyl]-pentan-3-ol, or 2-[1-(4-bromo-2,6-dimethylphenyl)-3-ethyl-5-methanesulfonyl-1H-pyrazol-4-ylmethyl]-3-ethoxymethyl-1,2,3,4-

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tetrahydroisoquinoline, all the tetrahydroisoquinoline-substituted derivatives of which being in the R absolute configuration at the 3-position within the tetrahydroisoquinoline group.

20. A composition for the treatment of (a) illnesses induced or facilitated by
5 corticotropin releasing factor or (b) inflammatory disorders such as rheumatoid arthritis, pain, asthma, psoriasis and allergies; anxiety disorders, including generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, and post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders, such as depression including major depression, and postpartum
10 depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; disorders of the immune system including immune dysfunction and human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such
15 as anorexia and bulimia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic syndrome hormone (ADH); and fertility problems, which comprises a compound according to claim 1 in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier.

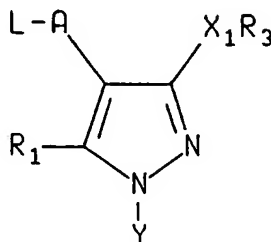
20 21. A method for the treatment of (a) illnesses induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as rheumatoid arthritis, pain, asthma, psoriasis and allergies; anxiety disorders, including generalized anxiety disorder, panic, phobias, obsessive-compulsive disorder, and post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia;
25 mood disorders, such as depression including major depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; disorders of the immune system including immune dysfunction and human immunodeficiency virus (HIV) infections; neurodegenerative
30 diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic syndrome hormone (ADH); and

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fertility problems, which comprises administering to a subject in need of such treatment a compound according to claim 1.

22. A compound of the formula

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wherein A is CH₂, R₁ is as defined in claim 1, R₃ is linear C₁-C₆ alkyl; branched C₃-C₈ alkyl; C₃-C₈ alkenyl wherein the double bond is not adjacent to the N or X₁ when X₁ is oxygen or sulfur; C₃-C₇ cycloalkyl (CH₂)_n wherein n is 0, 1, 2, 3 or 4 or (CH₂)_qQ₁R₆ wherein q is 0, 1 or 2, Q₁ is O, S, NH, N(C₁-C₆ alkyl) or a covalent bond, and R₆ is hydrogen, linear C₁-C₆ alkyl, branched C₃-C₈ alkyl, C₃-C₈ alkenyl, C₃-C₈ cycloalkyl, or C₃-C₆ cycloalkyl (CH₂)_n wherein n is 0 to 4, with the proviso that when q is 1, then X₁ and Q₁ can not both be a heteroatom;

X₁ is a covalent bond, CH₂NR, wherein R is hydrogen or linear C₁-C₆ alkyl, O, or S;

20

Y is phenyl which is substituted by from one to three of fluoro, chloro, bromo, formyl, C₁-C₆ alkyl, C₃-C₁₀ branched alkyl, C₁-C₆ alkoxy or trifluoromethyl, or by one of hydroxy, iodo, cyano, nitro, amino, NH(C₁-C₄ alkyl), N(C₁-C₄)(C₁-C₂ alkyl), COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂, NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C₁-C₄ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may contain one double or triple bond; thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benisothiazolyl, isoxazolyl, benisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or piperidinyl, each of which may be substituted by one to three of any one of fluoro, chloro, bromo, or methyl, or one of trifluoromethyl; and

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L is chloro, bromo, iodo, hydroxy, $O(C=O)(C_1-C_6 \text{ alkyl})$, $OSO_2(C_1-C_6 \text{ alkyl})$, $OSO_2\text{aryl}$ wherein said aryl is phenyl which may be substituted by one to three of fluoro, chloro, bromo, hydroxy, $O(C_1-C_6 \text{ alkyl})$, SH, $S(C_1-C_6 \text{ alkyl})$, amino, $NH(C_1-C_6 \text{ alkyl})$, $N(C_1-C_6 \text{ alkyl})_2$, or one of iodo, nitro or cyano.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 95/00318

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/12 C07D231/18 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,94 13661 (PFIZER INC.) 23 June 1994 see the whole document ---	1-22
X	JOURNAL OF MEDICINAL CHEMISTRY, vol.27, no.12, December 1984, WASHINGTON US pages 1559 - 1565 W.K. ANDERSON ET AL. 'Synthesis and Evaluation of Furan, Thiophene,, and Azole Bis[(carbamoyloxy)methyl] Derivatives as Potential Antineoplastic Agents' see page 1559, column 2, compounds no. 6, 10a and 10b ---	22
A	US,A,5 063 245 (MARY E. ABREU ET AL.) 5 November 1991 cited in the application see the whole document -----	1,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 July 1995

Date of mailing of the international search report

27. 07. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 95/00318

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 21 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched incompletely: 1-18, 20-22
Please see attached sheet ./.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

As the drafting of claims 1 and 22 (intermediates) encompasses such an enormous amount of compounds, a complete search is not possible on economic grounds (see WIPO: "PCT Search Guidelines", November 18, 1992, Part B, Chapter III, item 2).

Therefore, the search has been limited to the compounds of claim 1 wherein:

Y = (optionally) 2,4,6-tri-substituted phenyl; and

Z = one of (a), (b), (d)-(f), (h) and (i);

The intermediates of claim 22 have not been searched completely.

Moreover, it is to be noted, that the statement on page 10 of the description (concerning the extended definition of the moiety A) has not been taken into consideration for the purpose of the search.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 95/00318

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9413661	23-06-94	AU-B- 5141393 CN-A- 1093363 FI-A- 935672 HU-A- 65822	04-07-94 12-10-94 18-06-94 28-07-94
US-A-5063245	05-11-91	NONE	